

Metabolic Reprogramming of Immune Cells in Cancer Progression

Subhra K. Biswas^{1,*}

¹Singapore Immunology Network (SIgN), Agency for Science, Technology & Research (A*STAR), #04-06 Immunos, 8A Biomedical Grove, Singapore 138648, Singapore

*Correspondence: subhra_biswas@immunol.a-star.edu.sg

<http://dx.doi.org/10.1016/j.immuni.2015.09.001>

Immune cells play a key role in host defense against infection and cancer. Upon encountering danger signals, these cells undergo activation leading to a modulation in their immune functions. However, recent studies reveal that immune cells upon activation also show distinct metabolic changes that impact their immune functions. Such metabolic reprogramming and its functional effects are well known for cancer cells. Given that immune cells have emerged as crucial players in cancer progression, it is important to understand whether immune cells also undergo metabolic reprogramming in tumors and how this might affect their contribution in cancer progression. This emerging aspect of tumor-associated immune cells is reviewed here, discussing metabolic reprogramming of different immune cell types, the key pathways involved, and its impact on tumor progression.

Introduction

The role of immune cells in cancer progression is well-recognized. Inflammation and immune evasion are considered as hallmarks of cancer progression, highlighting the direct involvement of immune cells (Hanahan and Weinberg, 2011). Supporting this fact, macrophages, which represent one of the major immune infiltrates in solid tumors, influence various aspect of cancer progression, e.g., survival and proliferation of cancer cells, angiogenesis, metastasis, cancer-related inflammation, and immunosuppression (Biswas and Mantovani, 2010; Qian and Pollard, 2010). Similarly, other studies have indicated the involvement of almost every immune cell type including T cells, B cells, NK cells, NKT cells, basophils, neutrophils, dendritic cells (DCs), and myeloid-derived suppressor cells (MDSCs) in the regulation of cancer progression (Bindea et al., 2013; Biswas and Mantovani, 2010; Hanahan and Coussens, 2012). These observations have led to a major interest in characterizing the immune-microenvironment in cancer bearers with an aim to design immunotherapies that target specific immune subsets or their associated molecules in cancer (Bindea et al., 2013; Quail and Joyce, 2013).

Recent studies have revealed that immune cells possess distinct metabolic characteristics that influence their immunological functions. For example, macrophage polarization is related to distinct metabolic characteristics pertaining to energy metabolism, iron metabolism, and lipid metabolism (Biswas and Mantovani, 2010; Jha et al., 2015). Similarly, alterations in glucose and amino acid metabolism were reported for DCs and T cells upon activation (Pearce and Pearce, 2013). Taken together, these studies indicate that metabolic reprogramming is an important feature of immune cell activation.

Metabolic reprogramming has been suggested as a key hallmark of cancer progression (Hanahan and Weinberg, 2011; Ward and Thompson, 2012). Cancer cells undergo an alteration in their mode of energy metabolism in order to fulfill the bioenergetic and biosynthetic needs for rapid cell proliferation, as well as to adapt to the tumor microenvironment. While such metabolic alterations in cancer cells has been long known, a key question

that has not been investigated to depth is whether tumor-associated immune cells also undergo metabolic alterations during cancer progression. This is a pertinent question given the integral role of immune cells in cancer and their metabolic characteristics in other scenarios (e.g., infection, metabolic syndrome). This issue is reviewed here, highlighting the importance of metabolic reprogramming in the regulation of tumor-associated immune cell functions. In addition, some key molecular determinants that mediate the metabolic reprogramming in these cells and the therapeutic implications that might arise from these findings are also discussed.

Metabolic Reprogramming of Cancer Cells

Cancer cells need to fulfill their bioenergetic and biosynthetic demands to support rapid proliferation. To do so, they alter their energy metabolism to a glycolytic mode, even under aerobic conditions, for rapid energy generation. This aerobic form of glycolysis is also known as Warburg effect (Ward and Thompson, 2012). Thus, tumor cells get most of their energy through high consumption of glucose and its conversion into lactic acid by glycolysis, as opposed to mitochondrial oxidative phosphorylation in normal cells (Figure 1). The glycolytic switch is also a useful adaptation to survive in the hypoxic tumor microenvironment. The shift to glycolysis is triggered by various mechanisms reviewed elsewhere (Cairns et al., 2011; Ward and Thompson, 2012). For example, growth-factor signaling activates phosphoinositol 3-kinase (PI3K)-AKT, which induces the expression of glucose transporters (e.g., GLUT1) and the activation of glycolytic enzymes (e.g., HK2, PFKFB3). Mechanistically, PI3K-AKT signaling activates mammalian target of rapamycin (mTOR), which in turn activates the transcription factor, hypoxia-inducible factor 1 (HIF1). HIF1 cooperates with other transcription factors or oncogenes such as c-Myc, p53, or Oct1 to induce the expression of glycolytic genes including *GLUT1*, *HK2*, *PFKFB3*, *LDHA*, and suppressors of tricarboxylic acid (TCA) cycle such as PDK (Cairns et al., 2011; Semenza, 2003; Ward and Thompson, 2012). Moreover, mutations in TCA cycle enzymes such as

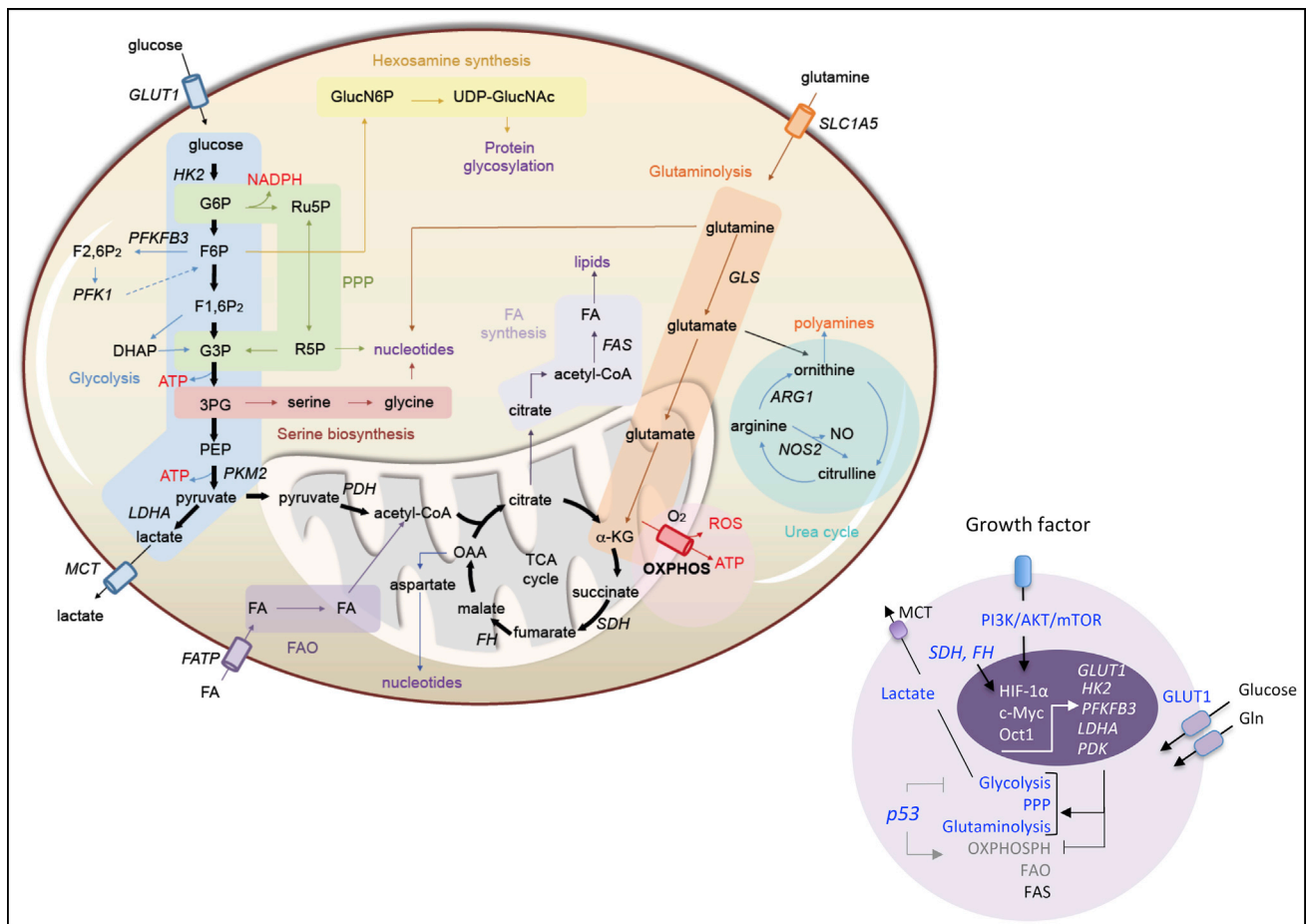


Figure 1. An Overview of Cellular Metabolic Pathways in a Cancer Cell

This diagram depicts some important cellular metabolic pathways and their components. Bold arrows indicate glycolysis and TCA cycle pathway. FA, fatty-acid; FAS, fatty acid synthase; PDH, pyruvate dehydrogenase. Inset (bottom right panel) shows an overview of key metabolic pathways and their associated molecules in cancer cells. Blue, black, and grey fonts indicate upregulated, sustained, and inhibited metabolic components, respectively. SDH, FH, and p53 refer to their mutated versions. Grey lines represent downregulated pathway.

succinate dehydrogenase (SDH) or fumarate hydratase (FH) also contribute to the inhibition of this pathway while promoting glycolysis through HIF1 activation. Collectively, these events culminate in the metabolic reprogramming of cancer cells to a predominantly glycolytic mode of energy metabolism (Figure 1).

Cancer cells require high concentrations of glutamine, which is necessary for supporting robust cell proliferation. Through the process of glutaminolysis, glutamine is converted to glutamate by glutaminase (GLS) and then to α -ketoglutarate (α -KG), which enters the TCA cycle to contribute to amino acid, nucleotide, and fatty-acid biosynthesis (Figure 1). Mechanistically, c-Myc plays an important role in promoting glutaminolysis in these cells (Gao et al., 2009; Wise et al., 2008). In addition, glutamine can also get converted to glutathione and thus contribute to the redox state.

Cancer cells undergo changes in their lipid metabolism acquiring a lipogenic phenotype. The enzyme monoacylglycerol lipase (MAGL) is highly expressed in cancer cells, where it regulates a pro-tumorigenic lipid network that supports tumor growth (Nomura et al., 2010). On the basis of the various metabolic changes discussed above, metabolic reprogramming of cancer

cells is indeed a hallmark of cancer progression (Hanahan and Weinberg, 2011; Ward and Thompson, 2012).

Metabolic Reprogramming of Immune Cells in Cancer

Recent evidence indicates metabolism as an important regulator of immune cell phenotype and function (Biswas and Mantovani, 2012; Ghesquiere et al., 2014; Pearce and Pearce, 2013). Because immune cells are crucial in tumor progression, it is important to understand how metabolic alterations in these cells regulate their pro- or anti-tumor properties.

Macrophages

Macrophages are versatile innate immune cells that contribute to diverse situations including host defense, homeostasis, and pathology. Although they show phenotypic and functional diversity, initial studies with defined *in vitro* stimuli have indicated two main macrophage activation or polarization phenotypes. For example, inflammatory stimuli such as interferon- γ (IFN- γ)+LPS induce macrophages to an M1 phenotype characterized by production of inflammatory cytokines (e.g., interleukin-12 [IL-12], tumor necrosis factor [TNF], IL-6, IL-1), reactive nitrogen and oxygen intermediates (RNI, ROI), and microbicidal functions (Biswas and

Mantovani, 2010). In contrast, anti-inflammatory stimuli such as IL-4, IL-13, IL-10, and glucocorticoid or immune complexes (IC)+LPS induce macrophages to an M2 phenotype characterized by decreased production of inflammatory cytokines, increased production of anti-inflammatory cytokines (e.g., IL-10), and factors that mediate immunosuppression and tissue remodeling. However, under *in vivo* situations such clearcut phenotypes are often blurred. Therefore, a multi-dimensional rather than a dichotomous (M1-M2) view of macrophage activation states was proposed recently wherein these cells integrate environmental signals in a stimulus-specific manner to induce specific functional outcomes (Xue et al., 2014). This necessitates a common framework to describe macrophage activation states (Murray et al., 2014).

Macrophages represent a major component of the lymphoreticular infiltrates in solid tumors and play a crucial role in cancer progression (Biswas et al., 2013; Murdoch et al., 2008; Qian and Pollard, 2010). On the one hand, macrophages by producing RNI, ROI, and inflammatory cytokines (e.g., TNF, IL-1, IL-6) contribute to genetic alterations and cancer-related inflammation that leads to tumorigenesis, as noted for many chronic-inflammation-induced cancers (Biswas et al., 2013; Grivennikov et al., 2010; Mantovani et al., 2008). On the other hand, these cells by producing anti-inflammatory cytokines (IL-10, TGF- β), cathepsins, and metalloproteases (MMPs) promote immunosuppression, extracellular matrix remodeling, tumor cell extravasation, and metastasis in established tumors, as well as regulate response to chemotherapy (Biswas et al., 2013; Grivennikov et al., 2010; Mantovani et al., 2008; Quail and Joyce, 2013; Ruffell et al., 2014). Macrophages by producing various pro-angiogenic molecules (e.g., EGF, VEGFA) also serve as important regulators of tumor angiogenesis (Murdoch et al., 2008). Although tumor-associated macrophages (TAMs) are generally described as an M2-like population, evidence suggesting an inflammatory (M1-like) phenotype or a phenotype with overlapping inflammatory and immunosuppressive features have also been reported (Franklin et al., 2014; Mantovani et al., 2002; Qian and Pollard, 2010). In fact, a functional plasticity of TAMs has been proposed, wherein macrophages show an inflammatory phenotype in the early phase of tumor establishment, while displaying an immunosuppressive phenotype in the later phase of tumor progression (Biswas et al., 2013) (Figure 2A). This is consistent with the functional diversity of these cells, the complex and dynamic nature of tumor microenvironmental signals *in vivo*, and the stage and type of cancer involved.

Polarized macrophages show distinct modes of glucose metabolism. For example, murine macrophages treated with the M1 stimuli IFN γ +LPS or LPS alone induced increased glycolysis, whereas exposure to M2 stimuli IL-4 induced increased oxidative phosphorylation (Rodriguez-Prados et al., 2010; Tannahill et al., 2013; Vats et al., 2006). Similarly, human monocytes upon β -glucan stimulation switched to a glycolytic mode, with concomitant reduction of oxidative phosphorylation (Cheng et al., 2014). The shift to glycolysis is mediated through the AKT-mTOR-HIF1 α pathway. In murine macrophages, LPS-induced shift to glycolysis results in the accumulation of the TCA cycle intermediate, succinate, which via the transcription factor HIF1 α induces the expression of the inflammatory cytokine IL-1 β (Tannahill et al., 2013). Glycolysis also induces TNF

expression in macrophages (Dietl et al., 2010). Together, these observations suggest glycolysis to regulate the inflammatory phenotype of macrophages.

TAMs show a “smoldered” inflammatory phenotype that promotes cancer-related inflammation (Mantovani et al., 2008). Importantly, TAMs accumulate in hypoxic areas of tumors where they express HIF1 α (Burke et al., 2003). Because many glycolytic genes such as *GLUT1*, *HK2*, *PFKFB3*, and *PGK1* are regulated by HIF1 α (Semenza et al., 1994), it makes sense that TAMs in such hypoxic areas of tumors preferentially utilize a glycolytic metabolism to mediate their inflammatory phenotype and support cancer-related inflammation. This is consistent with the role of HIF1 α in myeloid cell-mediated inflammation (Cramer et al., 2003). Moreover, HIF1 α activation induces RNI production by macrophages, while the glycolytic shift attenuates TCA cycle activity and mitochondrial respiration leading to enhanced ROS production (Peyssonnaux et al., 2005; Tannahill et al., 2013). Indeed, macrophages at the onset of inflammation-induced cancers, through RNI and ROS production can induce genetic instability and malignant transformation (Mantovani et al., 2008) (Figure 2A). On the basis of this, one might speculate that macrophages at the early stages of tumor onset preferentially utilize a glycolytic mode of energy metabolism to induce cancer-related inflammation and tumorigenesis (Figure 2A). A shift to glycolysis also serves as an adaptation for survival in the hypoxic tumor microenvironment.

Lactic acid is an important end-product of glycolysis. Increased glycolysis in TAMs, tumor cells, and other stromal cells (e.g., cancer-associated fibroblast, CAFs) would result in lactic acid accumulation in the tumor microenvironment (Ghesquiere et al., 2014). Lactic acid polarizes TAMs to a tumor-promoting phenotype characterized by the expression of arginase 1 (ARG1), VEGFA, and several M2 markers via HIF1 α activation (Colegio et al., 2014). Lactic acid can also activate Axl and Tie-2 receptors that drive an immunosuppressive and pro-angiogenic macrophage phenotype, supporting tumor promotion (Lemke and Lu, 2003; Lewis et al., 2007; Ruan and Kazlauskas, 2013). In contrast, tumor-derived lactic acid was reported to upregulate the pro-inflammatory cytokine IL-23 in human macrophages and murine TAMs from B16 melanoma, upon BCG treatment (Shime et al., 2008). Such opposite effects might be explained by the dynamic changes in lactic acid levels in growing tumors, which could induce differential macrophage responses in line with their functional plasticity in tumors (Biswas and Mantovani, 2010).

IL-4 is a well-known M2-polarizing macrophage stimulus. In PyMT-MMTV-driven spontaneous mammary carcinoma, Th2 cell-derived IL-4 polarized TAMs to an immunosuppressive (M2) phenotype (DeNardo et al., 2009). Because IL-4 promotes oxidative phosphorylation in macrophages (Vats et al., 2006), it might be speculated that TAMs in such tumors preferentially utilize oxidative phosphorylation instead of glycolysis.

Given the heterogeneity and dynamic nature of tumor microenvironment across different cancers, as well as different stages of the same cancer, it is quite likely that the mode of glucose metabolism in TAMs might also vary across these conditions. For example, TAMs from the early inflammatory phase of cancer onset might show glycolysis, while those in the later stages of cancer might show oxidative phosphorylation (Figure 2A). The shift to oxidative phosphorylation could be mediated by IL-4 from Th2 cells that infiltrate established tumors, as well as by other factors

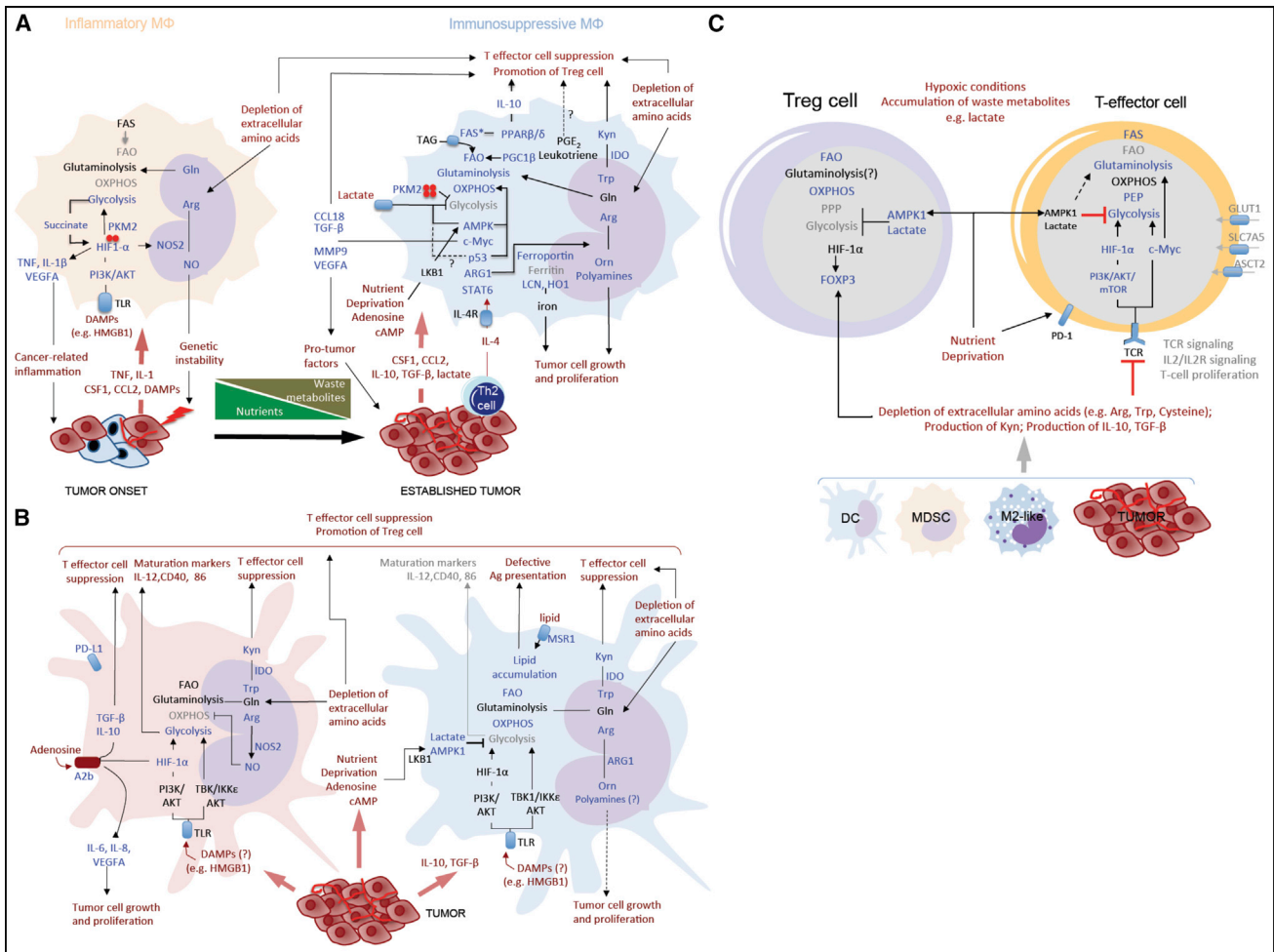


Figure 2. Metabolic Reprogramming of TAMs, TADCs, and T Cells and Their Altered Functions during Tumor Progression

An overview of the possible alterations in key metabolic processes, their component molecules, and its effect on pro-tumor functions for the indicated immune cell type is presented.

(A) Proposed metabolic shift in TAMs during tumor progression. During tumor onset, inflammatory macrophages through a glycolytic shift, HIF1 α activation, and an inhibited OXPHOSP mediate the expression of NO, ROI, IL-1 β , and TNF, to support genetic instability and cancer-related inflammation that leads to tumorigenesis. HIF1 α -induced expression of the angiogenic molecule VEGFA is also shown. In TAMs from established tumors, AMPK activation via nutrient deprivation, lactate accumulation, Th2-derived IL-4 (which activates c-Myc, p53, STAT6, PGC1 β), and activated PKM2 suppresses glycolysis, while upregulating OXPHOSP. This induces immunosuppressive macrophages that promote tumor growth. Changes in amino acid, iron, and fat metabolism that contribute to this process are also indicated.

(B) TADCs also show metabolic alterations during tumor progression. TADCs encounter tumor-derived DAMPs and hypoxia to upregulate glycolysis via an early TBK1-IKK ϵ and/or later PI3K-AKT-HIF1 α pathway. HIF1 α impairs DC maturation and upregulates A2b and NO expression (which inhibits OXPHOSP). Adenosine-A2b interaction induces an immunosuppressive and pro-tumor cytokines. The growing tumor progressively imposes nutrient deprivation, which activates AMPK in TADCs. This together with lactate accumulation leads to possible inhibition of glycolysis and upregulation of OXPHOSP in the TADCs. Amino acid uptake from the tumor microenvironment, its metabolism, and MSR1-mediated lipid accumulation further promotes immunosuppressive events to support tumor growth.

(C) Tumor microenvironment inhibits T effector cells and promotes Treg development. Depletion of extracellular amino acids (via uptake by tumor and other stromal cells), lactate accumulation, and nutrient deprivation-induced AMPK activation inhibits TCR signaling and its downstream glycolysis (indicated by red T symbol) in T effector cells (e.g., CD8⁺ cytotoxic T cells). This results in inhibition of proliferation and effector functions. Inhibition of glycolysis by AMPK, activation of OXPHOSP and FAO, and tumor microenvironment-derived factors (e.g., TGF- β , IL-10, Kyn, and hypoxia) instead promotes Treg development. This supports immune evasion and tumor growth. Black arrows and blue font in T-effector cell represent their metabolic state following activation through TCR-CD3 and CD28. However, these (except AMPK) are inhibited in tumor settings as mentioned above. In (A) and (B), although two different phenotypes of TAMs and TADCs are indicated for easy depiction, some of these characteristics may overlap in vivo due to the plasticity of these cells and multiplicity of tumor microenvironmental stimuli. Blue, black, and grey fonts indicate upregulated, sustained, and inhibited metabolic components, respectively. Dashed lines indicate likely (unproven) interactions. OXSPHOS: Oxidative phosphorylation; Arg, Arginine; Orn, Ornithine; Gln, glutamine; Trp, tryptophan; Kyn, Kynurenine; FAS, Fatty acid synthesis; FAS^{*}, Fatty acid synthase.

like lactic acid. In fact, lactic acid accumulation inhibits glycolysis, as well as induces an immunosuppressive and tissue remodeling macrophage phenotype, as discussed above (Colegio et al., 2014; Dietl et al., 2010). Another example is the glycolytic enzyme

pyruvate kinase, PKM2, which in its inactive dimeric form binds to HIF1 α and helps in IL-1 β expression in inflammatory macrophages, whereas in its active tetrameric form inhibits glycolysis, driving macrophages to an immunosuppressive, M2 phenotype

(Palsson-McDermott et al., 2015). It is possible that during tumor onset, inflammatory TAMs induce PKM2 expression, which upon subsequent activation (in its tetrameric form) switches these cells to an immunosuppressive (M2) phenotype in the established tumors (Figure 2A). It would be interesting to investigate whether TAMs actually display such metabolic plasticity and whether this is a cause or an effect of their functional plasticity in course of tumor progression.

Polarized macrophages display distinct modes of L-arginine metabolism (Rath et al., 2014). IFN γ +LPS-stimulated macrophages upregulate inducible nitric oxide synthase (iNOS or NOS2), which catalyzes the conversion of L-arginine into nitric oxide (NO) and L-citrulline (Figure 2A). In contrast, IL-4-treated macrophages upregulate ARG1 (Liver type) which catalyzes the conversion of L-arginine to L-ornithine and synthesis of polyamines (Modolell et al., 1995). These distinct modes of arginine metabolism have distinct functional consequences with macrophage NO production showing microbicidal and tumoricidal effects (Stuehr and Nathan, 1989), whereas ARG1-mediated polyamine production support cell proliferation, collagen synthesis, and tissue remodeling, relevant to tumor growth (Chang et al., 2001). Indeed, tumor-promoting TAMs from murine fibrosarcoma, Lewis lung carcinoma, B16 melanoma, and BW-Sp3 model show elevated ARG1 expression (Biswas et al., 2008; Sharda et al., 2011). In addition, Arg1 expression by TAMs can also mediate T cell immunosuppression (Kusmartsev and Gabrilovich, 2005), as discussed in the myeloid-derived suppressor cells (MDSCs) section. In a different setting, interaction with tumor cells induced Toll-like receptor (TLR)1-mediated NO expression by macrophages, which was instrumental in supporting post-radiotherapeutic tumor re-growth (Ryu et al., 2015).

Another important metabolic pathway in macrophages is the glutamine–glutamate pathway. Macrophages have high rates of glutamine utilization and express high levels of glutaminase, a key enzyme in glutamine metabolism. Early in vitro experiments indicated glutamine to be essential for cytokine production (e.g., TNF, IL-1, IL-6), antigen presentation, and phagocytosis in murine macrophages (Newsholme, 2001). Recent metabolic profiling demonstrated a preferential enrichment of several metabolites and genes of the glutamine metabolism (glutaminolysis) pathway (e.g., glutamate, AKG, *GPT2*, and *GATM*) in IL-4-induced M2 macrophages (Jha et al., 2015). In these cells, glutamine was essential for supporting an active TCA cycle and the UDPGlcNAc synthesis pathway, which is required for N-glycosylation. Accordingly, glutamine regulated the expression of M2 markers like the N-glycosylated receptor CD206, as well as IRF4, KLF4, and CCL22. Supporting these observations, TAMs from Lewis lung carcinoma, which show an M2 phenotype, also displayed higher gene expression of glutamine metabolism enzymes, transaminase (*GPT*), and glutamine synthetase (*GLUL*) (Colegio et al., 2014). However, whether and how glutamine metabolism regulates the tumor-promoting functions of TAMs needs to be clarified in future studies. The metabolism of other amino acids such as tryptophan in tumor associated myelomonocytic cells is discussed under MDSCs section (see below).

Macrophages can alter their lipid metabolism in response to distinct microenvironmental stimuli (Dennis et al., 2010; Martinez et al., 2006). For example, IL-4-activated mouse macrophages

upregulate fatty-acid uptake and fatty-acid oxidation (FAO), whereas this is suppressed in IFN γ +LPS-activated macrophages (Odegaard and Chawla, 2011). Uptake of triacylglycerol (TAG) and their subsequent lysosomal lipolysis were found to be essential for FAO and M2 activation in these IL-4-treated macrophages (Huang et al., 2014). Mechanistically, IL-4 via STAT6 triggered the expression of coactivator peroxisome proliferator-activated receptor (PPAR) γ -coactivator-1 β (PGC-1 β), which orchestrated the switch to mitochondrial respiration and FAO (Odegaard and Chawla, 2011). The nuclear receptors peroxisome proliferator activated receptor (PPAR) and liver X receptor (LXR) mediate macrophage response to lipids, discussed further in the next section. Polarized macrophages also show distinct changes in arachidonic acid metabolism with IFN γ +LPS-treated macrophages upregulating cyclooxygenase 2 (COX2) and microsomal isoform of PGE synthase (mPGES), but downregulating COX1, whereas IL-4-treated macrophages displaying the reverse trend, as detailed elsewhere (Biswas and Mantovani, 2012; Martinez et al., 2006; Mosca et al., 2007).

In a tumor setting, macrophages undergo changes in their lipid profile. A study in Lewis lung carcinoma showed differential lipid profiles in macrophages and cancer cells (Poczobutt et al., 2013). Leukotriene (LTB $_4$, LTC $_4$, LTD $_4$) production was mainly from myelomonocytic cells, whereas prostaglandin (PGE $_2$, PGD $_2$, PGF $_2$) production was from both myelomonocytic and cancer cells. Moreover, alveolar macrophages and infiltrating TAMs differed in eicosanoid profiles, with the former expressing COX1 (not COX2), 5-lipoxygenase and leukotrienes, while the latter expressing COX2 and prostaglandins. In the same tumor model, expression of fatty-acid synthase in TAMs polarized these cells to an IL-10-expressing, pro-tumor phenotype (Park et al., 2015). In another study, E-FABP-expressing TAMs were shown to produce high levels of IFN- β through upregulation of lipid droplet formation (Zhang et al., 2014). This IFN- β was instrumental for recruitment of NK cells and anti-tumor activity. These evidences suggest differential lipid metabolism in TAMs leading to pro- or anti-tumor functions, although the mechanism linking lipid metabolism to the functional outcome remains unclear.

Iron homeostasis is an important metabolic aspect of macrophages. Polarized macrophages show differential modes of iron metabolism. IFN γ +LPS-treated M1 macrophages express low levels of the iron exporter, ferroportin, but high levels of H-ferritin, which involved in iron storage (Cairo et al., 2011). Conversely, IL-4-treated M2 macrophages express low levels of H-ferritin, but high levels of ferroportin. In line with this profile, M1 macrophages are believed to favor iron sequestration and hence restrict bacterial and cancer growth, whereas M2 macrophages favor iron release which promotes tissue repair and tumor cell proliferation (Cairo et al., 2011; Recalcati et al., 2010). Supporting this concept, upregulation of another iron releasing protein, lipocalin (LCN) in TAMs supported the proliferation of human breast cancer cells (Jung et al., 2015). The iron-releasing enzyme, hemoxygenase-1 (HO-1) metabolizes heme to carbon monoxide, biliverdin, and ferrous iron. In a 4T1 mammary carcinoma model, suppression of HO-1 in TAMs was shown to skew their polarization from an M2 to an M1 phenotype that correlated with reduced tumor growth (Deng et al., 2013). Furthermore, intracellular iron level by regulating prolyl hydroxylases controls the stability of HIF1 α that is crucial for the survival and pro-tumor

function of TAMs (Maxwell et al., 1999). Taken together, the above findings provide ample evidences for the regulation of macrophage pro-tumor function by iron metabolism (Figure 2A).

Dendritic Cells

DCs are professional antigen-presenting cells that bridge innate and adaptive immunity. Upon sensing danger signals such as pathogen-associated or tissue-damage-related stimuli, immature DCs get activated and undergo maturation, which involves an upregulation of antigen-presenting molecules (e.g., major histocompatibility complex, MHCII, CD80, CD86, CD40), cytokines (e.g., IL-12), and chemokine receptors (e.g., CCR7). Matured DCs migrate to the lymphoid organs where they present antigen and activate a T cell response. In contrast to this scenario, DCs can also promote immune tolerance and immune evasion under certain circumstances. For example, DCs from tumor bearers (i.e., tumor associated DCs, TADCs) show an impaired ability to trigger immune response, while promoting immunosuppression (Apetoh et al., 2011; Dong and Bullock, 2014; Tran Janco et al., 2015). Accumulation of immature DCs, decreased number of functionally competent DCs, and matured DCs with impaired functions have been reported for several murine and human cancers (Gabrilovich et al., 2012). Although the mechanism(s) behind the impaired functionality of TADCs is still not well understood, a new perspective to the problem emerges with recent data on metabolic regulation of DC functions (Malinarich et al., 2015; Pearce and Everts, 2015; Ravindran et al., 2014).

DCs utilize oxidative phosphorylation under resting state, but shift to a glycolytic metabolism upon activation (Figure 2B, left panel). During the early phase of activation by TLR ligands, glycolysis is necessary for inducing an activation phenotype characterized by the upregulation of CD40, CD86, and IL-12p40, whereas during the later phase, glycolysis is dispensable for activation but necessary for DC survival (Krawczyk et al., 2010). Concomitant with the increased glycolysis activated DCs show a decrease in oxidative phosphorylation. The decreased oxidative phosphorylation is suggested to be mediated by NOS2-induced NO production (which inhibits the electron transport chain enzyme, cytochrome *c* oxidase) and activation of PI3K-AKT pathway (which inhibits AMP-activated protein kinase, a key regulator of oxidative phosphorylation) in the TLR-stimulated DCs. Collectively, these findings indicate glycolysis as key metabolic regulator of DC activation.

In the tumor microenvironment, various factors might impair the activation, maturation, and function of TADC. For example, the effect of hypoxia on DCs is not fully understood. In mice studies, hypoxia enhanced DC maturation (Jantsch et al., 2008). This involved the accumulation of HIF1 α , induction of glycolysis-related HIF target genes and increased glycolysis. In contrast, hypoxia impaired the maturation and migration of human monocyte-derived DCs (Mancino et al., 2008). This apparent contradiction might be explained by the fact that hypoxia induces progressive accumulation of metabolites like adenosine and lactic acid in the tumor microenvironment, which might negatively impact DC activation. Indeed, hypoxia upregulated adenosine receptor (A2b) on human DCs and switched them to a Th2 promoting phenotype (Yang et al., 2010). The interaction of adenosine-adenosine receptor impairs DC differentiation and function. Such DCs show impaired allostimulatory activity, enhanced expression of IL-6, COX2, TGF- β , IL-10, IL-8,

and VEGFA, and promoted tumor growth (Novitskiy et al., 2008). IL-10 and TGF- β would support T regulatory (Treg) cells, as reported for tumor-conditioned DCs (Dumitriu et al., 2009) (Figure 2B, left panel).

TADCs upregulate the immune checkpoint receptor PD-1 and its ligand PD-L1 (Tran Janco et al., 2015). Because PD-L1 is a HIF1 α target gene (Noman et al., 2014), it not difficult to speculate that tumor hypoxia would induce PD-L1 on DCs and propagate immune evasion (Figure 2B, left panel). Lactic acid also induces an impaired phenotype in DCs, similar to the TADCs (Gottfried et al., 2006). Moreover, in the tumor microenvironment, rapidly growing cancer cells impose nutrient competition and accumulation of metabolites like adenosine, which might trigger the metabolic sensor AMP-activated protein kinase (AMPK) in TADCs. AMPK is known to promote oxidative phosphorylation and inhibit glycolysis (Figure 2B right panel). This might provide a possible metabolic explanation for the impaired activation of TADCs. In support, tolerogenic DCs display a metabolic signature of increased oxidative phosphorylation that regulates their tolerogenic function (Malinarich et al., 2015). Future metabolic studies in TADCs should clarify whether they actually switch from glycolysis to oxidative phosphorylation in course of tumor progression.

TADCs through the expression of amino acid metabolism enzymes such as ARG1, NOS2, and Indoleamine 2,3-dioxygenase (IDO) mediate immunosuppression (Figure 2B). Like macrophages and MDSCs, ARG1 and IDO expression in TADCs exerts depletion of arginine and tryptophan in the tumor microenvironment, which has inhibitory effects on CD8⁺ T cell response and survival (Tran Janco et al., 2015), see MDSC section for further details. In addition, vitamin A metabolism to retinoic acid in TADCs was recently shown to drive Treg cell and tolerogenic response in melanoma (Hong et al., 2015).

Modulation of lipid metabolism such as de novo fatty-acid synthesis during DC activation affects ER and golgi expansion that impacts their antigen-presenting ability (Everts et al., 2014). TADCs express scavenging receptors like MSR1, which facilitate lipid uptake and accumulation (Herber et al., 2010). Lipid accumulation in these cells in turn impairs DC functions like tumor antigen presentation and allogeneic T cell response. It is tempting to speculate whether switching of TADCs from glycolysis to oxidative phosphorylation in the nutrient-deficient microenvironment of established tumors might favor fatty-acid synthesis and lipid accumulation, thereby contributing to their tolerogenic state. Nutrient starvation in tumor microenvironment also induces ER stress. Interestingly, the ER stress response factor XBP1 was shown to induce abnormal lipid accumulation via triglyceride biosynthetic program in TADCs, impairing its ability to support anti-tumor T cell response, thereby promoting ovarian cancer progression (Cubillos-Ruiz et al., 2015).

Despite their role in tumor promotion, DCs—due to their inherent capacity to present antigen and trigger an immune response—have been studied extensively in the context of tumor vaccines to boost an anti-tumor response (Apetoh et al., 2011). More recently, vaccines were shown to upregulate the nutrient sensor GCN2 in DCs to induce a CD8⁺ T cell response (Ravindran et al., 2014). How vaccine-mediated modulation of DC metabolism might contribute to their anti-tumor response would be interesting to study.

T Cells

T cells are key players in the host immune response to cancer. On the one hand, activated CD8⁺ T cells exert a direct and potent cytotoxic effect on tumor cells. On the other hand, activated CD4⁺ T cells differentiate into effector subtypes that either support or repress cancer growth. For example, CD4⁺ Th1 cells through IFN- γ secretion can activate macrophages and NK cells to induce an anti-tumor response, whereas CD4⁺ Th2 cells and Treg cells can promote tumor-induced immunosuppression. Depending on the context, Th17 cells can either support or inhibit tumor progression (Bailey et al., 2014).

T cells show distinct changes in metabolism depending on their activation and differentiation, reviewed extensively elsewhere (Pearce and Pearce, 2013; Siska and Rathmell, 2015). Naive T cells generate most of their energy through FAO, oxidative phosphorylation, and low levels of glutamine metabolism during the quiescence state. However, upon activation, these cells (differentiating into T-effector cells) have increased bioenergetic and biosynthetic needs to support rapid proliferation. To meet this, they increase nutrient uptake (e.g., glucose, amino acids) and upregulate glycolysis and glutaminolysis, while suppressing FAO (Figure 2C, right panel). However, oxidative phosphorylation is still maintained. Glutaminolysis and increased Pentose Phosphate Pathway (PPP) contribute to biosynthetic purposes, while glycolysis is required for T cell effector functions (Chang et al., 2013). Mechanistically, downstream of T cell receptor (TCR) and CD28, a PI3K-AKT-mTOR pathway activates transcription factors like HIF1 α and c-Myc (Siska and Rathmell, 2015). This in turn upregulates glucose transporters (GLUT1), metabolic enzymes (e.g., HK2), and amino-acid transporters (e.g., solute carrier proteins SLC7A5), which facilitate glycolysis and glutamine metabolism (glutaminolysis). Recently, TCR-dependent uptake of glutamine and leucine was reported to be mediated by the amino acid transporter ASCT2, which in turn led to mTOR activation and the development of Th1, Th17, and inflammatory T cell response (Nakaya et al., 2014). Interestingly, Treg cells and memory CD8⁺ T cells depend largely on oxidative phosphorylation for their energy metabolism (see below) (Figure 2C, left panel). The importance of amino-acid metabolism pertaining to arginine, tryptophan, glutamine, and cysteine on T cell effector function is discussed in the MDSC section. Fatty-acid metabolism is also an important regulator of T cell differentiation with de novo fatty-acid synthesis and FAO promoting T effector and Treg cell development, respectively (Lochner et al., 2015). De novo fatty-acid synthesis through acetyl-CoA carboxylase (ACC) was shown to be critical for Th17 cell differentiation, while preventing a Treg cell phenotype (Berod et al., 2014). Generation and survival of CD8⁺ memory T cells requires oxidative metabolism and FAO (van der Windt et al., 2012). These cells concurrently use fatty acid synthesis and FAO to meet their metabolic demands (O'Sullivan et al., 2014). In agreement, TAG synthesis was implicated in CD8⁺ memory T cell survival (Cui et al., 2015). Mechanistically, an orphan protein, lymphocyte expansion molecule (LEM) has recently been reported to control oxidative phosphorylation and mitochondrial ROS production in CD8⁺ T cells, thereby boosting memory T cell numbers and protective response against virus and cancer (Okoye et al., 2015).

High glycolytic activity of proliferating tumor cells coupled with the poor vasculature within tumors can induce amino acid and nutrient depletion. Such a situation would impair TCR signaling, glycolytic metabolism and the anti-tumor effector functions of T cells (Figure 2C, right panel). However, Treg cells, which mainly rely on FAO rather than glycolysis, can survive under these conditions and exert their immunosuppressive effect (Macintyre et al., 2014; Michalek et al., 2011) (Figure 2C, left panel). In fact, expansion of Treg cells has been linked to the activation of AMPK, a sensor of nutrient stress. In addition, accumulation of metabolic wastes such as lactate and amino acid metabolic products like kynurenine can also suppress T cell activation and cytotoxic activity, while promoting Treg cells (Siska and Rathmell, 2015). Furthermore, tumor hypoxia via HIF1 α can promote the expansion of Treg cells and induction of PD-L1 (Ben-Shoshan et al., 2008; Noman et al., 2014). Taken together, these observations indicate how the tumor microenvironment might shape the metabolic reprogramming of T cells, thereby modulating their effector functions to support immunosuppression (Figure 2C).

MDSCs

MDSCs are a heterogeneous group of immature myelomonocytic cells that are functionally defined by their potent immunosuppressive activity on T cells (Gabrilovich et al., 2012). These cells expand greatly in tumor bearers and were originally characterized by a CD11b⁺Gr1⁺ phenotype in tumor-bearing mice. MDSCs are classified into monocytic MDSCs and granulocytic MDSCs, both of which can induce suppression of antigen-activated CD8⁺ T cells.

Amino acid metabolism and oxidative stress play a pivotal role in mediating the suppressive activity of MDSCs on T cells. This is mediated by mainly two mechanisms: (1) depletion of amino acids essential to T cells and (2) generation of oxidative stress via reactive species (Gabrilovich et al., 2012) (Figure 3).

MDSCs can deplete L-arginine through its metabolism via ARG1 expression. Similarly, MDSCs can cause L-cysteine deprivation through its sequestering (Srivastava et al., 2010). Depletion of these amino acids leads to the downregulation of ζ -chain of the T cell receptor and inhibition of T cell proliferation. MDSCs, like macrophages and DCs, express the inducible enzyme IDO, which catalyzes tryptophan metabolism along the kynurenine pathway (Martinez et al., 2006; Munn et al., 1999). Thus, IDO exerts its inhibitory effect on T cells via tryptophan deprivation (by metabolizing it), as well as by inducing the expansion of Treg cells (Grohmann and Bronte, 2010; Saxena et al., 2007). Corroborating with this, MDSCs were found to promote expansion of Treg cells in B cell lymphoma (Serafini et al., 2008).

MDSCs subsets by expressing NOS2, ARG1, and NADPH oxidase induce the production of RNI (e.g., NO, peroxynitrite) and ROI (e.g., H₂O₂) (Gabrilovich et al., 2012). These reactive species downregulate the ζ -chain of TCR and IL-2 receptor signaling, inhibiting T cell activation and proliferation. Monocytic MDSCs mainly induce their inhibitory effect via NO while granulocytic MDSCs do so via ROI.

While the crucial role of nitrogen metabolism in regulating the immunosuppressive functions of MDSCs in tumor settings is well established, relatively little is known about the other metabolic pathways in these cells. Enhanced carbon metabolism (glycolysis, glutaminolysis, and TCA activity) and its crosstalk with

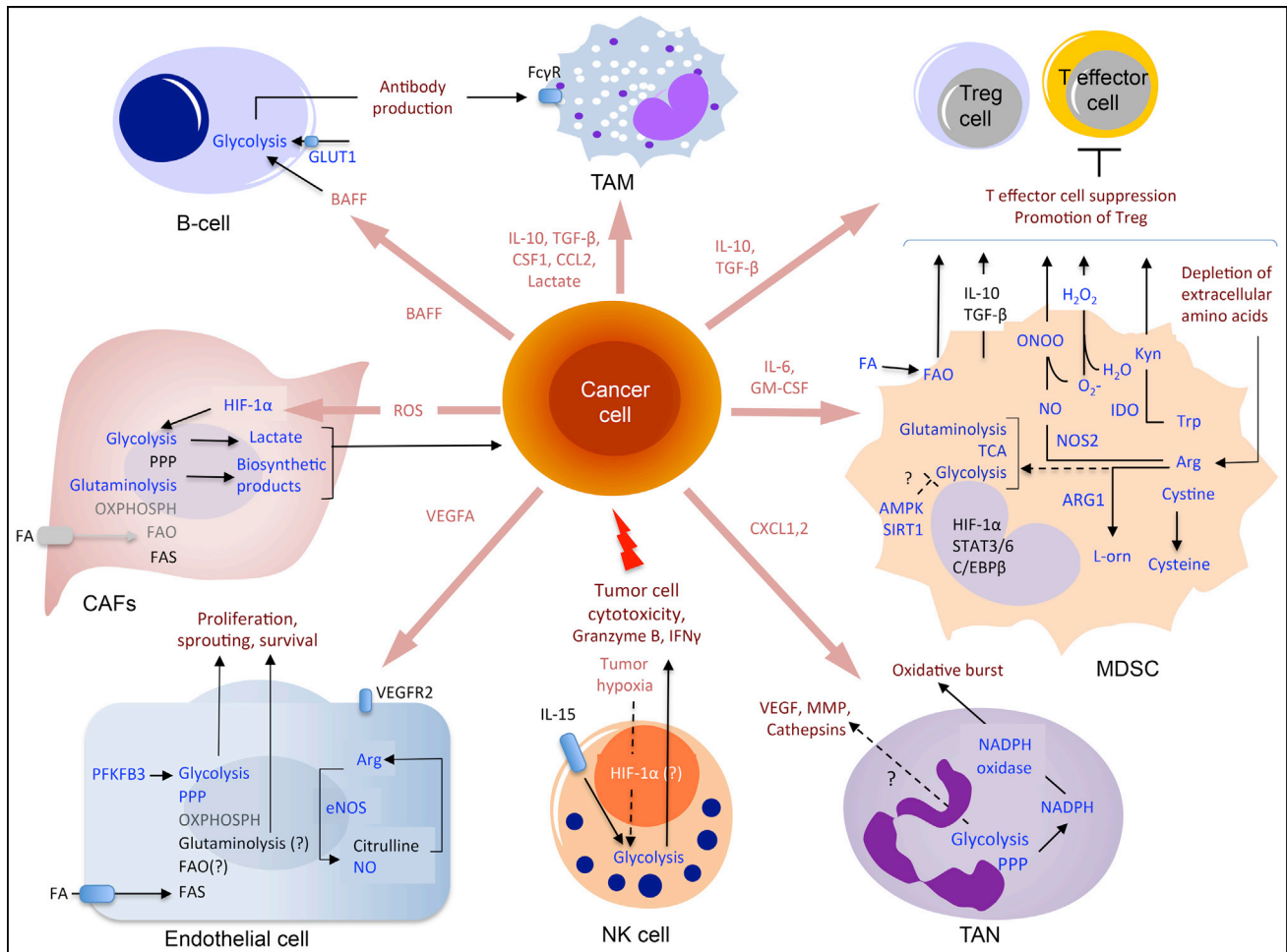


Figure 3. Metabolic Crosstalk between Cancer Cells and Indicated Stromal Cells Showing Their Metabolic Reprogramming and Altered Functions in Tumors

Metabolic alterations in the indicated non-immune (e.g., CAFs, endothelial cells) and immune stromal cells (MDSCs, B cells, NK cells, neutrophils) are presented. Blue, black, and grey fonts indicate upregulated, sustained, and inhibited metabolic components, respectively. Dashed lines indicate likely (unproven) interactions. Arg, Arginine; Orn, Ornithine; Gln, glutamine; Trp; tryptophan; Kyn, Kynurenine; FAS, Fatty acid synthesis.

arginine metabolism was noted during MDSC maturation, but its relationship with the increased expression of AMPK and SIRT, which are known to interfere with glycolysis, needs to be clarified (Hammami et al., 2012; Liu et al., 2014) (Figure 3). Recently, increased fatty-acid uptake and FAO was also demonstrated to regulate the immunosuppressive function of tumor infiltrating MDSCs (Hossain et al., 2015).

Neutrophils

Tumors are known to release chemokines that recruit neutrophils. Tumor-associated neutrophils (TANs) can have both pro- and anti-tumor effects (Mantovani et al., 2011). In the absence of tumor-derived TGF-β, TANs encouraged CD8+ T cells response and anti-tumor activity, whereas in the presence of TGF-β, exhibited tumor promoting activity. TANs produce several factors like arginase 1, ROI, cathepsins, MMPs, and pro-angiogenic cytokines, which promote tumor growth, angiogenesis, and metastasis.

Metabolically, neutrophils are strongly committed to aerobic glycolysis and PPP as the dominant mode of energy metabolism

(Figure 3). This is in line with the fact that these cells possess few mitochondria, which are however are not used in ATP production, but for maintaining redox balance, essential for cell survival. Glycolysis and PPP contribute to neutrophil functionality. For example, PPP pathway produces NADPH, which is a cofactor for NADPH oxidase, a key enzyme mediating neutrophil microbicidal functions. Studies on glucose-6-phosphate transporter deficiency in human neutrophils also implicated glycolysis in the regulation of important neutrophil functions like oxidative burst and chemotaxis (Jun et al., 2014). Another important function of neutrophils is the formation of neutrophil extracellular traps (NETs), a mixture of DNA, histones and anti-microbial peptides that traps and kills bacteria. Glucose uptake, glycolysis, and a metabolic shift toward PPP are essential for NETs formation (Azevedo et al., 2015; Rodriguez-Espinosa et al., 2015). NETs can sequester circulating tumor cells and promote metastasis (Cools-Lartigue et al., 2013). Moreover, NETs were observed to accumulate in the vasculature of tumor-bearing mice, which was associated with proinflammatory adhesion molecules and

cytokines, contributing to cancer-induced organ failure (Cedervall et al., 2015). Collectively, these data provide some suggestions as to how metabolic change in neutrophils by regulating functions like NETs might contribute to tumor progression. Further characterization of neutrophil function relating to cancer and their regulation by cell-intrinsic metabolism is now needed.

Natural Killer Cells

Natural killer (NK) cells by producing IFN- γ and cytotoxic molecules like granzyme play an integral role in activating an anti-tumor T cell response and tumor cell killing. A recent study in primary murine NK cells showed them to mainly utilize oxidative phosphorylation under resting conditions and upon short-term activation (Keppel et al., 2015). However, upon prolonged culture with high-dose of IL-15, NK cells showed increased glycolytic metabolism. This is consistent with another recent study, which confirmed NK cells to show heightened glycolysis upon activation (Donnelly et al., 2014). Glycolysis was shown to regulate granzyme B and IFN- γ expression by activated NK cells. In the tumor microenvironment, hypoxia and IL-15 would promote glycolysis in NK cells, supporting their anti-tumor activity (Figure 3). It would be interesting to investigate how different tumor-associated stimuli impact NK activation and metabolism, thereby modulating their anti-tumor response.

B Cells

B cells via antibody production and immune complexes can modulate myeloid cells function to support tumor progression (Andreu et al., 2010; de Visser et al., 2005). Recently, LPS or antigen-stimulated activation of B cells was shown to trigger a balanced increase in both glycolysis and mitochondrial metabolic activity (Caro-Maldonado et al., 2014). However, BAFF-mediated chronic stimulation poised them for rapid induction of aerobic glycolysis and a Glut1-dependent metabolic reprogramming that was necessary for antibody production (Figure 3). Mechanistically, c-Myc but not HIF1 α was implicated in mediating the metabolic changes in B cells. Given that many tumors express BAFF, it remains to be seen how B cell metabolic reprogramming might affect their contribution to tumor progression.

Other Stromal Cells

In addition to the immune cells discussed above, NKT cells, innate lymphoid cells, basophils, and mast cells have been shown to contribute to tumor progression (Biswas and Mantovani, 2012). However, the metabolic control of these cell types in the tumor microenvironment remains unknown. Endothelial cells and cancer associated fibroblasts (CAFs) are two important stromal cell types that have a strong influence on tumor associated immune cells, tumor cells, and tumor progression (Ghesquiere et al., 2014). Endothelial cells are highly glycolytic cells that depend on this pathway for almost 85% of their energy (Figure 3). Glycolysis, PPP, and glutamine metabolism regulate vascular sprouting, proliferation, and survival of these cells. PFKFB3 is a key regulator of glycolysis in these cells. Similarly, proliferating CAFs display increased glycolytic flux and glutamine metabolism, but possess a truncated TCA cycle at citrate. In fact, CAFs are “hijacked” by the cancer cells for the production of lactic acid, amino acids, and ketone bodies, which supply nutrients for the cancer cells. Cancer cells in turn produce ROS that activates HIF1 α in CAFs to maintain their glycolytic metabolism (Figure 3). Recently, reprogramming of glucose and

amino acid metabolism in CAFs via a p62-mTOR1-c-Myc pathway was linked to tumor promotion through increased ROS and IL-6 production (Valencia et al., 2014). A detailed account of the metabolic reprogramming of endothelial cells and CAFs is presented by Ghesquiere et al. (2014).

Molecular Determinants of Metabolic Reprogramming of Immune Cells in Cancer

Accumulating evidence suggests the metabolic reprogramming of immune cells in tumor settings. But the molecular mechanism(s) that drives this process is far from clear. We discuss below a few important molecules that regulate metabolism in immune cells and how they might mediate the metabolic reprogramming of these cells in the tumor microenvironment.

PI3K-AKT Pathway

Stimulation of immune cells like macrophages, DCs by TLR ligands (e.g., LPS, CpG), or T cells via TCR-CD3 and CD28 signaling triggers activation of the PI3K-AKT pathway. Depending on the cell type, PI3K induces the expression of glucose transporter GLUT1 (in DCs, macrophages) and key glycolysis enzymes like HK2 and phosphofructokinase 2 (PFK2). Accordingly, the role of PI3K-AKT in glycolysis is reported for all the three cell types mention above (Chang et al., 2009; Cheng et al., 2014; Krawczyk et al., 2010; Siska and Rathmell, 2015) (Figures 2 and 3). Because tumor microenvironmental factors like versican, HMGB1, and DAMPs can stimulate the TLR pathway, it is reasonable to speculate that signaling through TLR and other receptors (G protein coupled receptors, receptor tyrosine kinases) would activate PI3K-AKT in infiltrating myeloid cells like TAMs leading to glycolysis and the promotion of cancer-related inflammation (Schmid et al., 2011). PI3K-AKT activation in TAMs and mast cells was shown to promote colitis-induced cancer (Khan et al., 2013). In a pancreatic and mammary cancer model, PI3K activation in tumor infiltrating CD11b⁺ myeloid cells was implicated in resistance to anti-angiogenic therapy (Rivera et al., 2015). PI3K-AKT activation in GM-CSF-derived DCs induced the negative regulator disabled-2 adaptor protein (DAB2), which inhibited CTL response against tumors and promotes immunosuppressive phenotypes (Ahmed et al., 2015). Such a phenotype is reminiscent of TADCs. PI3K-AKT is also a survival signal that would promote the survival of immune cells in the hostile tumor microenvironment. Collectively, these evidences suggest PI3K-AKT pathway to be an important regulator of glycolysis in immune cells, as well as to drive these cells to a tumor promoting phenotype.

mTOR

mTOR is an important regulator of metabolism in immune cells that couples nutrient sensing to metabolic outcomes like glycolysis, fatty-acid synthesis, and protein synthesis. mTOR mediates metabolic processes like glycolysis by enhancing the expression of HIF1 α (Cheng et al., 2014; Howell and Manning, 2011) (Figures 1 and 2). mTOR is a downstream target of AKT signaling not only in DCs and T cells (Krawczyk et al., 2010), but in all mammalian cells. However, its role in DCs is still not clear. mTOR inhibition by rapamycin in murine GM-CSF-derived BMDCs enhanced immunostimulatory and anti-tumor activity, whereas its inhibition in human monocyte-derived and plasmacytoid DCs downregulated pro-inflammatory cytokines and CD8⁺ T cell response (Dong and Bullock, 2014). In macrophages, constitutive

activation of mTOR promoted an immunosuppressive and tissue remodeling M2 phenotype that was in line with the phenotype of TAMs in established tumors (Byles et al., 2013). However, promotion of this phenotype was linked to PI3K inhibition by mTOR through a negative feedback loop. In T cells, TCR signaling can activate mTOR. mTOR activation sustained glycolysis and effector functions in CD8⁺ T cells, as well as differentiation of T cells into distinct subsets like Th1, Th2, or Th17 (Siska and Rathmell, 2015). In contrast, mTOR inhibited the development of Treg cells, which rely mainly on FAO (Michalek et al., 2011). mTOR also contributes to the survival of immune types. Although the tumor microenvironmental stimuli, which induce mTOR activation in immune subsets, is not yet well understood, it is conceivable that mTOR activation in these tumor-associated immune cells would modulate their metabolism to support survival, differentiation, and tumor-promoting functions.

AMPK

AMPK is a well-known molecule of metabolic interest and a key regulator of oxidative phosphorylation. Because IL-4-activated macrophages preferentially induce oxidative phosphorylation, this and other anti-inflammatory factors like IL-10, TGF- β , and STAT3 were shown to induce rapid AMPK activation in macrophages, driving them to an immunosuppressive phenotype (Sag et al., 2008; Zhu et al., 2015). Conversely, inflammatory stimuli like LPS that preferentially induce glycolysis, suppressed AMPK activation in macrophages (Sag et al., 2008). In DCs, AMPK activation was shown to suppress glucose consumption and LPS-induced IL-12p40 expression, indicating impaired maturation (Krawczyk et al., 2010). In T cells, AMPK activation has been implicated in diverse functions like suppression of T effector function, promotion of T regulatory function, and the generation of CD8⁺ memory T cells (Michalek et al., 2011; Pearce and Pearce, 2013; Siska and Rathmell, 2015) (Figure 2C). Importantly, a key role of AMPK is nutrient sensing via its activation by LKB1.

Based on the above facts, it is conceivable that various factors in the tumor microenvironment such as nutrient deprivation, adenosine, and anti-inflammatory cytokines (e.g., IL-4, IL-10 and TGF- β) would induce AMPK activation in TAMs, TADCs, and infiltrating T cells (Figure 2). This in turn, would lead to a metabolic skewing of these cells toward oxidative phosphorylation, which supports their immunosuppressive phenotype, facilitating tumor growth. However, the role of AMPK might be more complex due to its involvement in Th1 and Th17 development and primary T cell responses to viral and bacterial infections in vivo, reported recently (Blagih et al., 2015). Whether these observations also hold true in cancer settings is still to be ascertained.

HIF1 α

HIF1 α is an important transcription factor that orchestrates response of mammalian cells to hypoxia (or low oxygen concentration). Other stimuli such as LPS, bacteria, and fungi also activate HIF1 α in monocytes, macrophages, and DCs (Cheng et al., 2014; Rius et al., 2008; Shalova et al., 2015; Tannahill et al., 2013). Hypoxia is a well-known tumor microenvironmental condition and tumor-infiltrating myeloid cells like TAMs and MDSCs demonstrate heightened expression of HIF1 α expression (Murdoch et al., 2008). HIF1 α is an important regulator of cellular metabolism and function in these cells. Several glycolysis-

related genes like *GLUT1*, *HK2*, and *PFKFB3* are direct target genes of HIF1 α (Semenza, 2003). Thus, HIF1 α activation in immune cells is closely linked to glycolysis (Figure 2). The role of HIF1 α in different immune cell types might vary. For example, HIF1 α induces inflammatory cytokines and “trained immunity” in LPS- and β -glucan-treated glycolytic macrophages, respectively (Cheng et al., 2014; Tannahill et al., 2013). HIF1 α also regulates angiogenic and tissue remodeling molecules (e.g., VEGFA and MMPs) and functions in monocytes and macrophages (Fang et al., 2009; Shalova et al., 2015). Thus, HIF1 α by driving inflammation, angiogenesis, and tissue remodeling is well-suited to orchestrate a tumor promoting phenotype in macrophages. However, it is not clear whether HIF1 α induces all these functions via a metabolic reprogramming through glycolysis. Interestingly, HIF1 α can also contribute to immunosuppression through tumor-derived lactic acid, induction of PD-L1 expression on MDSCs, MDSC differentiation, and expansion of Treg cells (Ben-Shoshan et al., 2008; Colegio et al., 2014; Corzo et al., 2010; Noman et al., 2014). Collectively, these observations suggest HIF1 α to regulate the functional plasticity of immune response during tumor progression. For example, during tumor onset, HIF1 α activation in TAMs might upregulate glycolytic metabolism and support cancer-related inflammation (via IL-1 β production), whereas in established tumors, HIF1 α expression in TAMs, MDSCs, DCs, and Treg cells would collectively promote angiogenesis and immunosuppression (via lactic acid, PD-L1 expression, adenosine-adenosine receptor interaction on DCs, etc.) to sustain tumor growth (Figures 2A–2C). This is in line with the recently described role of HIF1 α in driving the plasticity of human monocytes in sepsis (Shalova et al., 2015). Further studies on the temporal regulation of HIF1 α and metabolism will shed light on the link between metabolic and immunological plasticity of tumor infiltrating immune cells.

c-Myc

The oncogenic transcription factor c-Myc has a regulatory effect on multiple metabolic processes. For example, c-Myc in combination with HIF can induce the expression of glucose transporter and enzymes like lactate dehydrogenase A (LDHA) and pyruvate dehydrogenase kinase 1 (PDK1) to enhance glycolysis. c-Myc has a major contribution in glutamine metabolism in cancer (and stromal) cells by inducing the expression of glutamine transporters (e.g., SLC5A1) and glutaminase 1 (GLS1), the initial enzyme of glutaminolysis (Gao et al., 2009; Wise et al., 2008). In activated T cells, c-Myc controlled metabolic reprogramming by regulating their metabolic transcriptome and thereby impacting glycolysis, glutaminolysis, and polyamine synthesis (Wang et al., 2011). Moreover, c-Myc controls the M2 polarization and tumor-promoting function of TAMs by regulating pro-tumor factors like CCL18, TGF- β , VEGF, and MMP9 (Pello et al., 2012a; Pello et al., 2012b) (Figure 2A, right panel). However, what are the metabolic effects of c-Myc in TAMs and whether these metabolic events mediate the pro-tumor activity of these cells is not yet known.

p53

The transcription factor and tumor suppressor p53 is a regulator of metabolism. p53 regulates glucose metabolism in multiple ways: it induces expression of the glycolysis enzyme HK2, it suppresses glycolysis by upregulating molecules such as TP53-induced glycolysis and apoptosis regulator (TIGAR) and

Phosphatase and tensin homolog (PTEN), and also promotes oxidative phosphorylation (Cairns et al., 2011). Thus, in tumor cells, p53 loss would force a glycolytic pathway (Figure 1, inset), whereas in stromal cells like TAMs, where p53 is activated (Lowe et al., 2014), it should block glycolysis and support oxidative phosphorylation, although this is yet to be proven (Figure 2A, right panel). In support, p53 was recently implicated in regulation of M2 macrophage polarization (Li et al., 2015). It would be interesting to see how p53 impacts the metabolic characteristics of these polarized cells.

PPARs and LXRs

PPARs and LXRs are “lipid sensing” nuclear receptors that are activated by free fatty acids, eicosanoids, prostaglandins, or cholesterol metabolites. Upon activation, they bind to their target gene promoter, inducing or repressing its expression. PPAR γ was shown to regulate the alternative (or M2) activation of macrophages and metabolic homeostasis (Liao et al., 2011; Odegaard and Chawla, 2011). In a cancer setting, PPAR γ activation had an anti-tumor effect on cancer cells, whereas its activation in myeloid cells (e.g., macrophages) promoted lung tumor progression and metastasis (Li et al., 2011). PPAR δ has been implicated in the clearance of apoptotic cells (Odegaard and Chawla, 2011). This might be important in tumors, where dead cancer cells are believed to polarize TAMs. In lung cancer, tumor cells by inducing fatty-acid synthase and PPAR β/δ activation in TAMs polarizes them into an IL-10 expressing, pro-tumor phenotype (Park et al., 2015). Similarly, phagocytosis of apoptotic tumor cells (which contain oxysterols) would activate LXRs in macrophages resulting in an immunosuppressive phenotype (Traversari et al., 2014). In fact, LXR activation by tumor-derived oxysterol also suppresses DC migration and neutrophil recruitment into tumors, as well as interferes with tumor-infiltrating antigen-specific T cells, which results in tolerance and immunosuppression (Traversari et al., 2014). Whether PPARs and LXRs mediated these effects by modulating cell-intrinsic metabolism remains to be characterized. This might be possible because both these nuclear receptors regulate a number of glucose and lipid metabolism genes.

Besides the molecules described above, recent studies have revealed several other players. Compliments contribute to cancer-related inflammation by modulating tumor-infiltrating immune cells (e.g., TAMs) (Bonavita et al., 2015). Recent evidence implicates complements in regulating immune cell metabolism and their effector functions (Kolev et al., 2015). Thus, in tumors too, compliments might regulate the metabolism and function of infiltrating immune cells. MicroRNAs can also serve as metabolic regulators, since they are known to regulate energy metabolism in cancer cells, immune cells, and CAFs (Ghesquiere et al., 2014). Microbiota through the metabolism of bile acids, hormones, alcohol, and its metabolites (e.g., deoxycholic acid) can impact cancer progression (Schwabe and Jobin, 2013). However, whether these microbial metabolites regulate cancer promotion by polarizing the tumor-associated immune cells remains to be investigated.

Concluding Remarks and Therapeutic Implications

Metabolic changes in immune cells regulate their phenotype and function. This is also true for the tumor microenvironment. While tumor cells opt for metabolic changes like glycolysis to support

their biosynthetic and energetic needs for rapid proliferation and survival in hypoxic tumor microenvironments, evidence suggests that the infiltrating immune cells (e.g., TAMs, TADCs, MDSCs, T cells, neutrophils, B cells, and NK cells) also undergo metabolic alterations that contribute to their pro- or anti-tumor functions. These observations suggest (1) a metabolic dialog between tumor cells and these stromal immune cells and (2) a close link between metabolic reprogramming of immune cells and their plasticity during tumor growth. For example, during the onset of tumor, glycolytic metabolism in TAMs would induce inflammatory cytokines, RNI, and ROS production, which support oncogenic transformation and cancer-related inflammation. Later, in established tumors, nutrient deprivation and accumulation of metabolites like lactic acid and adenosine would induce oxidative phosphorylation in TAMs and DCs to drive them to an immunosuppressive phenotype. ARG1 and IDO activity in these cells and MDSCs also induce amino acid deprivation in the tumor microenvironment. Collectively, these events together with metabolic changes in T cells would inhibit anti-tumor T effector cell response, induce Treg cell response and mediate immunosuppression, thereby promoting tumor progression. A systematic profiling of tumor-associated immune subsets at a transcriptional, metabolic, and function level would shed light on several issues such as how metabolic changes regulate the transcriptional and functional phenotype of these cells, what are the common and divergent metabolic characteristics between these different immune cell types and tumor cells, and whether the metabolic characteristics of these cells remain stable or change in course of tumor progression, indicating a metabolic plasticity.

Mechanistically, various metabolites and metabolic regulators such as lactic acid, HIF1, c-Myc, AMPK, and mTOR, which control metabolic reprogramming of immune cells and tumor cells, are being tested for targeting. Drugs targeting lactate transporter MCT1 and MCT2 (Doherty and Cleveland, 2013) and AMPK (e.g., Metformin) are being evaluated for anti-tumor effects in preclinical models and in clinical trials (Kim et al., 2014). Interestingly, besides affecting tumor cells, Metformin has a direct effect on infiltrating immune cells: increasing CD8⁺ T cell recruitment, protecting them from apoptosis and exhaustion, increasing CD8⁺ memory T cells, and providing a better response to anti-cancer vaccines (Eikawa et al., 2015). The PD-1-PD-L1 pathway, a prominent target in cancer immunotherapy, also induces metabolic reprogramming of T cell metabolism (Patsoukis et al., 2015). Thus, future studies identifying metabolic targets common to cancer cells and tumor promoting immune cells will not only pave way for devising a two-pronged attack on cancer and its stroma but also open new options for “re-purposing” existing metabolic drugs. Using such drugs in combination with conventional chemotherapy is already being evaluated in pre-clinical settings.

ACKNOWLEDGMENTS

S.K.B. thanks S1gN (A*STAR) for the core funding and Dr. Irina N. Shalova for help with the figure preparation.

REFERENCES

Ahmed, M.S., Byeon, S.E., Jeong, Y., Miah, M.A., Salahuddin, M., Lee, Y., Park, S.S., and Bae, Y.S. (2015). Dab2, a negative regulator of DC

- immunogenicity, is an attractive molecular target for DC-based immunotherapy. *Oncol Immunology* 4, e984550.
- Andreu, P., Johansson, M., Affara, N.I., Pucci, F., Tan, T., Junankar, S., Korets, L., Lam, J., Tawfik, D., DeNardo, D.G., et al. (2010). FcR γ activation regulates inflammation-associated squamous carcinogenesis. *Cancer Cell* 17, 121–134.
- Apetoh, L., Locher, C., Ghiringhelli, F., Kroemer, G., and Zitvogel, L. (2011). Harnessing dendritic cells in cancer. *Semin. Immunol.* 23, 42–49.
- Azevedo, E.P., Rochael, N.C., Guimaraes-Costa, A.B., de Souza-Vieira, T.S., Ganiho, J., Saraiva, E.M., Palhano, F.L., and Foguel, D. (2015). A metabolic shift towards pentose phosphate pathway is necessary for amyloid fibril- and phorbol 12-myristate 13-acetate -induced neutrophil extracellular trap (NET) formation. *J Biol Chem.* 290, 22174–22183.
- Bailey, S.R., Nelson, M.H., Himes, R.A., Li, Z., Mehrotra, S., and Paulos, C.M. (2014). Th17 cells in cancer: the ultimate identity crisis. *Front. Immunol.* 5, 276.
- Ben-Shoshan, J., Maysel-Auslender, S., Mor, A., Keren, G., and George, J. (2008). Hypoxia controls CD4+CD25+ regulatory T-cell homeostasis via hypoxia-inducible factor-1 α . *Eur. J. Immunol.* 38, 2412–2418.
- Berod, L., Friedrich, C., Nandan, A., Freitag, J., Hagemann, S., Harmrolfs, K., Sandouk, A., Hesse, C., Castro, C.N., Bahre, H., et al. (2014). De novo fatty acid synthesis controls the fate between regulatory T and T helper 17 cells. *Nat. Med.* 20, 1327–1333.
- Bindea, G., Mlecnik, B., Tosolini, M., Kirilovsky, A., Waldner, M., Obenauf, A.C., Angell, H., Fredriksen, T., Lafontaine, L., Berger, A., et al. (2013). Spatio-temporal dynamics of intratumoral immune cells reveal the immune landscape in human cancer. *Immunity* 39, 782–795.
- Biswas, S.K., and Mantovani, A. (2010). Macrophage plasticity and interaction with lymphocyte subsets: cancer as a paradigm. *Nat. Immunol.* 11, 889–896.
- Biswas, S.K., and Mantovani, A. (2012). Orchestration of metabolism by macrophages. *Cell Metab.* 15, 432–437.
- Biswas, S.K., Sica, A., and Lewis, C.E. (2008). Plasticity of macrophage function during tumor progression: regulation by distinct molecular mechanisms. *J. Immunol.* 180, 2011–2017.
- Biswas, S.K., Allavena, P., and Mantovani, A. (2013). Tumor-associated macrophages: functional diversity, clinical significance, and open questions. *Semin. Immunopathol.* 35, 585–600.
- Blagih, J., Coulombe, F., Vincent, E.E., Dupuy, F., Galicia-Vazquez, G., Yurchenko, E., Raissi, T.C., van der Windt, G.J., Viollet, B., Pearce, E.L., et al. (2015). The energy sensor AMPK regulates T cell metabolic adaptation and effector responses in vivo. *Immunity* 42, 41–54.
- Bonavita, E., Gentile, S., Rubino, M., Maina, V., Papaït, R., Kunderfranco, P., Greco, C., Feruglio, F., Molgora, M., Laface, I., et al. (2015). PTX3 is an extrinsic oncosuppressor regulating complement-dependent inflammation in cancer. *Cell* 160, 700–714.
- Burke, B., Giannoudis, A., Corke, K.P., Gill, D., Wells, M., Ziegler-Heitbrock, L., and Lewis, C.E. (2003). Hypoxia-induced gene expression in human macrophages: implications for ischemic tissues and hypoxia-regulated gene therapy. *Am. J. Pathol.* 163, 1233–1243.
- Byles, V., Covarrubias, A.J., Ben-Sahra, I., Lamming, D.W., Sabatini, D.M., Manning, B.D., and Horng, T. (2013). The TSC-mTOR pathway regulates macrophage polarization. *Nat. Commun.* 4, 2834.
- Cairns, R.A., Harris, I.S., and Mak, T.W. (2011). Regulation of cancer cell metabolism. *Nat. Rev. Cancer* 11, 85–95.
- Cairo, G., Recalcati, S., Mantovani, A., and Locati, M. (2011). Iron trafficking and metabolism in macrophages: contribution to the polarized phenotype. *Trends Immunol.* 32, 241–247.
- Caro-Maldonado, A., Wang, R., Nichols, A.G., Kuraoka, M., Milasta, S., Sun, L.D., Gavin, A.L., Abel, E.D., Kelsoe, G., Green, D.R., and Rathmell, J.C. (2014). Metabolic reprogramming is required for antibody production that is suppressed in anergic but exaggerated in chronically BAFF-exposed B cells. *J. Immunol.* 192, 3626–3636.
- Cedervall, J., Zhang, Y., Huang, H., Zhang, L., Femel, J., Dimberg, A., and Olsson, A.K. (2015). Neutrophil Extracellular Traps Accumulate in Peripheral Blood Vessels and Compromise Organ Function in Tumor-Bearing Animals. *Cancer Res.* 75, 2653–2662.
- Chang, C.I., Liao, J.C., and Kuo, L. (2001). Macrophage arginase promotes tumor cell growth and suppresses nitric oxide-mediated tumor cytotoxicity. *Cancer Res.* 61, 1100–1106.
- Chang, M., Hamilton, J.A., Scholz, G.M., and Elsegood, C.L. (2009). Glycolytic control of adjuvant-induced macrophage survival: role of PI3K, MEK1/2, and Bcl-2. *J. Leukoc. Biol.* 85, 947–956.
- Chang, C.H., Curtis, J.D., Maggi, L.B., Jr., Faubert, B., Villarino, A.V., O'Sullivan, D., Huang, S.C., van der Windt, G.J., Blagih, J., Qiu, J., et al. (2013). Post-transcriptional control of T cell effector function by aerobic glycolysis. *Cell* 153, 1239–1251.
- Cheng, S.C., Quintin, J., Cramer, R.A., Shepardson, K.M., Saeed, S., Kumar, V., Giamarellos-Bourboulis, E.J., Martens, J.H., Rao, N.A., Aghajani-Refah, A., et al. (2014). mTOR- and HIF-1 α -mediated aerobic glycolysis as metabolic basis for trained immunity. *Science* 345, 1250684.
- Colegio, O.R., Chu, N.Q., Szabo, A.L., Chu, T., Rhebergen, A.M., Jairam, V., Cyrus, N., Brokowski, C.E., Eisenbarth, S.C., Phillips, G.M., et al. (2014). Functional polarization of tumour-associated macrophages by tumour-derived lactic acid. *Nature* 513, 559–563.
- Cools-Lartigue, J., Spicer, J., McDonald, B., Gowing, S., Chow, S., Giannias, B., Bourdeau, F., Kubes, P., and Ferri, L. (2013). Neutrophil extracellular traps sequester circulating tumor cells and promote metastasis. *J. Clin. Invest.* 123, 3446–3458.
- Corzo, C.A., Condamine, T., Lu, L., Cotter, M.J., Youn, J.I., Cheng, P., Cho, H.I., Celis, E., Quiceno, D.G., Padhya, T., et al. (2010). HIF-1 α regulates function and differentiation of myeloid-derived suppressor cells in the tumor microenvironment. *J. Exp. Med.* 207, 2439–2453.
- Cramer, T., Yamashita, Y., Clausen, B.E., Forster, I., Pawlinski, R., Mackman, N., Haase, V.H., Jaenisch, R., Corr, M., Nizet, V., et al. (2003). HIF-1 α is essential for myeloid cell-mediated inflammation. *Cell* 112, 645–657.
- Cubillos-Ruiz, J.R., Silberman, P.C., Rutkowski, M.R., Chopra, S., Perales-Puchalt, A., Song, M., Zhang, S., Bettigole, S.E., Gupta, D., Holcomb, K., et al. (2015). ER Stress Sensor XBP1 Controls Anti-tumor Immunity by Disrupting Dendritic Cell Homeostasis. *Cell* 161, 1527–1538.
- Cui, G., Staron, M.M., Gray, S.M., Ho, P.C., Amezcua, R.A., Wu, J., and Kaech, S.M. (2015). IL-7-Induced Glycerol Transport and TAG Synthesis Promotes Memory CD8(+) T Cell Longevity. *Cell* 161, 750–761.
- de Visser, K.E., Korets, L.V., and Coussens, L.M. (2005). De novo carcinogenesis promoted by chronic inflammation is B lymphocyte dependent. *Cancer Cell* 7, 411–423.
- DeNardo, D.G., Barreto, J.B., Andreu, P., Vasquez, L., Tawfik, D., Kolhatkar, N., and Coussens, L.M. (2009). CD4(+) T cells regulate pulmonary metastasis of mammary carcinomas by enhancing protumor properties of macrophages. *Cancer Cell* 16, 91–102.
- Deng, R., Wang, S.M., Yin, T., Ye, T.H., Shen, G.B., Li, L., Zhao, J.Y., Sang, Y.X., Duan, X.G., and Wei, Y.Q. (2013). Inhibition of tumor growth and alteration of associated macrophage cell type by an HO-1 inhibitor in breast carcinoma-bearing mice. *Oncol. Res.* 20, 473–482.
- Dennis, E.A., Deems, R.A., Harkewicz, R., Quehenberger, O., Brown, H.A., Milne, S.B., Myers, D.S., Glass, C.K., Hardiman, G., Reichart, D., et al. (2010). A mouse macrophage lipidome. *J. Biol. Chem.* 285, 39976–39985.
- Dietl, K., Renner, K., Dettmer, K., Timischl, B., Eberhart, K., Dorn, C., Hellerbrand, C., Kastenberger, M., Kunz-Schughart, L.A., Oefner, P.J., et al. (2010). Lactic acid and acidification inhibit TNF secretion and glycolysis of human monocytes. *J. Immunol.* 184, 1200–1209.
- Doherty, J.R., and Cleveland, J.L. (2013). Targeting lactate metabolism for cancer therapeutics. *J. Clin. Invest.* 123, 3685–3692.
- Dong, H., and Bullock, T.N. (2014). Metabolic influences that regulate dendritic cell function in tumors. *Front. Immunol.* 5, 24.
- Donnelly, R.P., Loftus, R.M., Keating, S.E., Liou, K.T., Biron, C.A., Gardiner, C.M., and Finlay, D.K. (2014). mTORC1-dependent metabolic reprogramming is a prerequisite for NK cell effector function. *J. Immunol.* 193, 4477–4484.

- Dumitriu, I.E., Dunbar, D.R., Howie, S.E., Sethi, T., and Gregory, C.D. (2009). Human dendritic cells produce TGF- β 1 under the influence of lung carcinoma cells and prime the differentiation of CD4+CD25+Foxp3+ regulatory T cells. *J. Immunol.* *182*, 2795–2807.
- Eikawa, S., Nishida, M., Mizukami, S., Yamazaki, C., Nakayama, E., and Udono, H. (2015). Immune-mediated antitumor effect by type 2 diabetes drug, metformin. *Proc. Natl. Acad. Sci. USA* *112*, 1809–1814.
- Everts, B., Amiel, E., Huang, S.C., Smith, A.M., Chang, C.H., Lam, W.Y., Redmann, V., Freitas, T.C., Blagih, J., van der Windt, G.J., et al. (2014). TLR-driven early glycolytic reprogramming via the kinases TBK1-IKK ϵ supports the anabolic demands of dendritic cell activation. *Nat. Immunol.* *15*, 323–332.
- Fang, H.Y., Hughes, R., Murdoch, C., Coffelt, S.B., Biswas, S.K., Harris, A.L., Johnson, R.S., Imityaz, H.Z., Simon, M.C., Fredlund, E., et al. (2009). Hypoxia inducible factors 1 and 2 are important transcriptional effectors in primary macrophages experiencing hypoxia. *Blood* *114*, 844–859.
- Franklin, R.A., Liao, W., Sarkar, A., Kim, M.V., Bivona, M.R., Liu, K., Pamer, E.G., and Li, M.O. (2014). The cellular and molecular origin of tumor-associated macrophages. *Science* *344*, 921–925.
- Gabrilovich, D.I., Ostrand-Rosenberg, S., and Bronte, V. (2012). Coordinated regulation of myeloid cells by tumours. *Nat. Rev. Immunol.* *12*, 253–268.
- Gao, P., Tchernyshyov, I., Chang, T.C., Lee, Y.S., Kita, K., Ochi, T., Zeller, K.I., De Marzo, A.M., Van Eyk, J.E., Mendell, J.T., and Dang, C.V. (2009). c-Myc suppression of miR-23a/b enhances mitochondrial glutaminase expression and glutamine metabolism. *Nature* *458*, 762–765.
- Ghesquiere, B., Wong, B.W., Kuchnio, A., and Carmeliet, P. (2014). Metabolism of stromal and immune cells in health and disease. *Nature* *511*, 167–176.
- Gottfried, E., Kunz-Schughart, L.A., Ebner, S., Mueller-Klieser, W., Hoves, S., Andreesen, R., Mackensen, A., and Kreutz, M. (2006). Tumor-derived lactic acid modulates dendritic cell activation and antigen expression. *Blood* *107*, 2013–2021.
- Grivennikov, S.I., Greten, F.R., and Karin, M. (2010). Immunity, inflammation, and cancer. *Cell* *140*, 883–899.
- Grohmann, U., and Bronte, V. (2010). Control of immune response by amino acid metabolism. *Immunol. Rev.* *236*, 243–264.
- Hammami, I., Chen, J., Murschel, F., Bronte, V., De Crescenzo, G., and Jolicoeur, M. (2012). Immunosuppressive activity enhances central carbon metabolism and bioenergetics in myeloid-derived suppressor cells in vitro models. *BMC Cell Biol.* *13*, 18.
- Hanahan, D., and Coussens, L.M. (2012). Accessories to the crime: functions of cells recruited to the tumor microenvironment. *Cancer Cell* *21*, 309–322.
- Hanahan, D., and Weinberg, R.A. (2011). Hallmarks of cancer: the next generation. *Cell* *144*, 646–674.
- Herber, D.L., Cao, W., Nefedova, Y., Novitskiy, S.V., Nagaraj, S., Tyurin, V.A., Corzo, A., Cho, H.J., Celis, E., Lennox, B., et al. (2010). Lipid accumulation and dendritic cell dysfunction in cancer. *Nat. Med.* *16*, 880–886.
- Hong, Y., Manoharan, I., Suryawanshi, A., Majumdar, T., Angus-Hill, M.L., Koni, P.A., Manicassamy, B., Mellor, A.L., Munn, D.H., and Manicassamy, S. (2015). beta-catenin promotes regulatory T-cell responses in tumors by inducing vitamin A metabolism in dendritic cells. *Cancer Res.* *75*, 656–665.
- Hossain, F., Al-Khami, A.A., Wyczechowska, D., Hernandez, C., Zheng, L., Reiss, K., Del Valle, L., Trillo-Tinoco, J., Maj, T., Zou, W., et al. (2015). Inhibition of Fatty Acid Oxidation Modulates Immunosuppressive Functions of Myeloid-Derived Suppressor Cells and Enhances Cancer Therapies. *Cancer Immunol. Res.* *1*–12.
- Howell, J.J., and Manning, B.D. (2011). mTOR couples cellular nutrient sensing to organismal metabolic homeostasis. *Trends Endocrinol. Metab.* *22*, 94–102.
- Huang, S.C., Everts, B., Ivanova, Y., O'Sullivan, D., Nascimento, M., Smith, A.M., Beatty, W., Love-Gregory, L., Lam, W.Y., O'Neill, C.M., et al. (2014). Cell-intrinsic lysosomal lipolysis is essential for alternative activation of macrophages. *Nat. Immunol.* *15*, 846–855.
- Jantsch, J., Chakravorty, D., Turza, N., Prechtel, A.T., Buchholz, B., Gerlach, R.G., Volke, M., Glasner, J., Warnecke, C., Wiesener, M.S., et al. (2008). Hypoxia and hypoxia-inducible factor-1 alpha modulate lipopolysaccharide-induced dendritic cell activation and function. *J. Immunol.* *180*, 4697–4705.
- Jha, A.K., Huang, S.C., Sergushichev, A., Lampropoulou, V., Ivanova, Y., Loghincheva, E., Chmielewski, K., Stewart, K.M., Ashall, J., Everts, B., et al. (2015). Network Integration of Parallel Metabolic and Transcriptional Data Reveals Metabolic Modules that Regulate Macrophage Polarization. *Immunity* *42*, 419–430.
- Jun, H.S., Weinstein, D.A., Lee, Y.M., Mansfield, B.C., and Chou, J.Y. (2014). Molecular mechanisms of neutrophil dysfunction in glycogen storage disease type Ib. *Blood* *123*, 2843–2853.
- Jung, M., Mertens, C., and Brune, B. (2015). Macrophage iron homeostasis and polarization in the context of cancer. *Immunobiology* *220*, 295–304.
- Keppel, M.P., Saucier, N., Mah, A.Y., Vogel, T.P., and Cooper, M.A. (2015). Activation-specific metabolic requirements for NK Cell IFN-gamma production. *J. Immunol.* *194*, 1954–1962.
- Khan, M.W., Keshavarzian, A., Gounaris, E., Melson, J.E., Cheon, E.C., Blatner, N.R., Chen, Z.E., Tsai, F.N., Lee, G., Ryu, H., et al. (2013). PI3K/AKT signaling is essential for communication between tissue-infiltrating mast cells, macrophages, and epithelial cells in colitis-induced cancer. *Clin. Cancer Res.* *19*, 2342–2354.
- Kim, J., Lim, W., Kim, E.K., Kim, M.K., Paik, N.S., Jeong, S.S., Yoon, J.H., Park, C.H., Ahn, S.H., Kim, L.S., et al. (2014). Phase II randomized trial of neoadjuvant metformin plus letrozole versus placebo plus letrozole for estrogen receptor positive postmenopausal breast cancer (METEOR). *BMC Cancer* *14*, 170.
- Kolev, M., Dimeloe, S., Le Friec, G., Navarini, A., Arbore, G., Povoleri, G.A., Fischer, M., Belle, R., Loeliger, J., Develiglu, L., et al. (2015). Complement Regulates Nutrient Influx and Metabolic Reprogramming during Th1 Cell Responses. *Immunity* *42*, 1033–1047.
- Krawczyk, C.M., Holowka, T., Sun, J., Blagih, J., Amiel, E., DeBerardinis, R.J., Cross, J.R., Jung, E., Thompson, C.B., Jones, R.G., and Pearce, E.J. (2010). Toll-like receptor-induced changes in glycolytic metabolism regulate dendritic cell activation. *Blood* *115*, 4742–4749.
- Kusmartsev, S., and Gabrilovich, D.I. (2005). STAT1 signaling regulates tumor-associated macrophage-mediated T cell deletion. *J. Immunol.* *174*, 4880–4891.
- Lemke, G., and Lu, Q. (2003). Macrophage regulation by Tyro 3 family receptors. *Curr. Opin. Immunol.* *15*, 31–36.
- Lewis, C.E., De Palma, M., and Naldini, L. (2007). Tie2-expressing Monocytes and Tumor Angiogenesis: Regulation by Hypoxia and Angiopoietin-2. *Cancer Res.* *67*, 1–4.
- Li, H., Sorenson, A.L., Poczobutt, J., Amin, J., Joyal, T., Sullivan, T., Crossno, J.T., Jr., Weiser-Evans, M.C., and Nemenoff, R.A. (2011). Activation of PPAR-gamma in myeloid cells promotes lung cancer progression and metastasis. *PLoS ONE* *6*, e28133.
- Li, L., Ng, D.S., Mah, W.C., Almeida, F.F., Rahmat, S.A., Rao, V.K., Leow, S.C., Laudisi, F., Peh, M.T., Goh, A.M., et al. (2015). A unique role for p53 in the regulation of M2 macrophage polarization. *Cell Death Differ.* *22*, 1081–1093.
- Liao, X., Sharma, N., Kapadia, F., Zhou, G., Lu, Y., Hong, H., Paruchuri, K., Mahabeshwar, G.H., Dalmás, E., Venticlef, N., et al. (2011). Kruppel-like factor 4 regulates macrophage polarization. *J. Clin. Invest.* *121*, 2736–2749.
- Liu, G., Bi, Y., Shen, B., Yang, H., Zhang, Y., Wang, X., Liu, H., Lu, Y., Liao, J., Chen, X., and Chu, Y. (2014). SIRT1 limits the function and fate of myeloid-derived suppressor cells in tumors by orchestrating HIF-1alpha-dependent glycolysis. *Cancer Res.* *74*, 727–737.
- Lochner, M., Berod, L., and Sparwasser, T. (2015). Fatty acid metabolism in the regulation of T cell function. *Trends Immunol.* *36*, 81–91.
- Lowe, J.M., Menendez, D., Bushel, P.R., Shatz, M., Kirk, E.L., Troester, M.A., Garantziotis, S., Fessler, M.B., and Resnick, M.A. (2014). p53 and NF-kappaB coregulate proinflammatory gene responses in human macrophages. *Cancer Res.* *74*, 2182–2192.
- Macintyre, A.N., Gerriets, V.A., Nichols, A.G., Michalek, R.D., Rudolph, M.C., Deoliveira, D., Anderson, S.M., Abel, E.D., Chen, B.J., Hale, L.P., and Rathmell, J.C. (2014). The glucose transporter Glut1 is selectively essential for CD4 T cell activation and effector function. *Cell Metab.* *20*, 61–72.

- Malinarich, F., Duan, K., Hamid, R.A., Bijn, A., Lin, W.X., Poidinger, M., Fairhurst, A.M., and Connolly, J.E. (2015). High mitochondrial respiration and glycolytic capacity represent a metabolic phenotype of human tolerogenic dendritic cells. *J. Immunol.* *194*, 5174–5186.
- Mancino, A., Schioppa, T., Larghi, P., Pasqualini, F., Nebuloni, M., Chen, I.H., Sozzani, S., Austyn, J.M., Mantovani, A., and Sica, A. (2008). Divergent effects of hypoxia on dendritic cell functions. *Blood* *112*, 3723–3734.
- Mantovani, A., Sozzani, S., Locati, M., Allavena, P., and Sica, A. (2002). Macrophage polarization: tumor-associated macrophages as a paradigm for polarized M2 mononuclear phagocytes. *Trends Immunol.* *23*, 549–555.
- Mantovani, A., Allavena, P., Sica, A., and Balkwill, F. (2008). Cancer-related inflammation. *Nature* *454*, 436–444.
- Mantovani, A., Cassatella, M.A., Costantini, C., and Jaillon, S. (2011). Neutrophils in the activation and regulation of innate and adaptive immunity. *Nat. Rev. Immunol.* *11*, 519–531.
- Martinez, F.O., Gordon, S., Locati, M., and Mantovani, A. (2006). Transcriptional profiling of the human monocyte-to-macrophage differentiation and polarization: new molecules and patterns of gene expression. *J. Immunol.* *177*, 7303–7311.
- Maxwell, P.H., Wiesener, M.S., Chang, G.W., Clifford, S.C., Vaux, E.C., Cockman, M.E., Wykoff, C.C., Pugh, C.W., Maher, E.R., and Ratcliffe, P.J. (1999). The tumour suppressor protein VHL targets hypoxia-inducible factors for oxygen-dependent proteolysis. *Nature* *399*, 271–275.
- Michalek, R.D., Gerriets, V.A., Jacobs, S.R., Macintyre, A.N., MacIver, N.J., Mason, E.F., Sullivan, S.A., Nichols, A.G., and Rathmell, J.C. (2011). Cutting edge: distinct glycolytic and lipid oxidative metabolic programs are essential for effector and regulatory CD4+ T cell subsets. *J. Immunol.* *186*, 3299–3303.
- Modolell, M., Corraliza, I.M., Link, F., Soler, G., and Eichmann, K. (1995). Reciprocal regulation of the nitric oxide synthase/arginase balance in mouse bone marrow-derived macrophages by TH1 and TH2 cytokines. *Eur. J. Immunol.* *25*, 1101–1104.
- Mosca, M., Polentarutti, N., Mangano, G., Apicella, C., Doni, A., Mancini, F., De Bortoli, M., Coletta, I., Polenzani, L., Santoni, G., et al. (2007). Regulation of the microsomal prostaglandin E synthase-1 in polarized mononuclear phagocytes and its constitutive expression in neutrophils. *J. Leukoc. Biol.* *82*, 320–326.
- Munn, D.H., Shafizadeh, E., Attwood, J.T., Bondarev, I., Pashine, A., and Mellor, A.L. (1999). Inhibition of T cell proliferation by macrophage tryptophan catabolism. *J. Exp. Med.* *189*, 1363–1372.
- Murdoch, C., Muthana, M., Coffelt, S.B., and Lewis, C.E. (2008). The role of myeloid cells in the promotion of tumour angiogenesis. *Nat. Rev. Cancer* *8*, 618–631.
- Murray, P.J., Allen, J.E., Biswas, S.K., Fisher, E.A., Gilroy, D.W., Goerdt, S., Gordon, S., Hamilton, J.A., Ivashkiv, L.B., Lawrence, T., et al. (2014). Macrophage Activation and Polarization: Nomenclature and Experimental Guidelines. *Immunity* *41*, 14–20.
- Nakaya, M., Xiao, Y., Zhou, X., Chang, J.H., Chang, M., Cheng, X., Blonska, M., Lin, X., and Sun, S.C. (2014). Inflammatory T cell responses rely on amino acid transporter ASCT2 facilitation of glutamine uptake and mTORC1 kinase activation. *Immunity* *40*, 692–705.
- Newsholme, P. (2001). Why is L-glutamine metabolism important to cells of the immune system in health, postinjury, surgery or infection? *J Nutr* *131*, 2515S–2522S, discussion 2523S–2514S.
- Noman, M.Z., Desantis, G., Janji, B., Hasmim, M., Karray, S., Dessen, P., Bronte, V., and Chouaib, S. (2014). PD-L1 is a novel direct target of HIF-1alpha, and its blockade under hypoxia enhanced MDSC-mediated T cell activation. *J. Exp. Med.* *211*, 781–790.
- Nomura, D.K., Long, J.Z., Niessen, S., Hoover, H.S., Ng, S.W., and Cravatt, B.F. (2010). Monoacylglycerol lipase regulates a fatty acid network that promotes cancer pathogenesis. *Cell* *140*, 49–61.
- Novitskiy, S.V., Ryzhov, S., Zaynagetdinov, R., Goldstein, A.E., Huang, Y., Tikhomirov, O.Y., Blackburn, M.R., Biaggioni, I., Carbone, D.P., Feoktistov, I., and Dikov, M.M. (2008). Adenosine receptors in regulation of dendritic cell differentiation and function. *Blood* *112*, 1822–1831.
- O'Sullivan, D., van der Windt, G.J., Huang, S.C., Curtis, J.D., Chang, C.H., Buck, M.D., Qiu, J., Smith, A.M., Lam, W.Y., DiPlato, L.M., et al. (2014). Memory CD8(+) T cells use cell-intrinsic lipolysis to support the metabolic programming necessary for development. *Immunity* *41*, 75–88.
- Odegaard, J.I., and Chawla, A. (2011). Alternative macrophage activation and metabolism. *Annu. Rev. Pathol.* *6*, 275–297.
- Okoye, I., Wang, L., Pallmer, K., Richter, K., Ichimura, T., Haas, R., Crouse, J., Choi, O., Heathcote, D., Lovo, E., et al. (2015). T cell metabolism. The protein LEM promotes CD8(+) T cell immunity through effects on mitochondrial respiration. *Science* *348*, 995–1001.
- Palsson-McDermott, E.M., Curtis, A.M., Goel, G., Lauterbach, M.A., Sheedy, F.J., Gleeson, L.E., van den Bosch, M.W., Quinn, S.R., Domingo-Fernandez, R., Johnston, D.G., et al. (2015). Pyruvate kinase M2 regulates Hif-1alpha activity and IL-1beta induction and is a critical determinant of the warburg effect in LPS-activated macrophages. *Cell Metab.* *21*, 65–80.
- Park, J., Lee, S.E., Hur, J., Hong, E.B., Choi, J.I., Yang, J.M., Kim, J.Y., Kim, Y.C., Cho, H.J., Peters, J.M., et al. (2015). M-CSF from Cancer Cells Induces Fatty Acid Synthase and PPARbeta/delta Activation in Tumor Myeloid Cells, Leading to Tumor Progression. *Cell Rep.* *10*, 1614–1625.
- Patsoukis, N., Bardhan, K., Chatterjee, P., Sari, D., Liu, B., Bell, L.N., Karoly, E.D., Freeman, G.J., Petkova, V., Seth, P., et al. (2015). PD-1 alters T-cell metabolic reprogramming by inhibiting glycolysis and promoting lipolysis and fatty acid oxidation. *Nat. Commun.* *6*, 6692.
- Pearce, E.J., and Everts, B. (2015). Dendritic cell metabolism. *Nat. Rev. Immunol.* *15*, 18–29.
- Pearce, E.L., and Pearce, E.J. (2013). Metabolic pathways in immune cell activation and quiescence. *Immunity* *38*, 633–643.
- Pello, O.M., Chevre, R., Laoui, D., De Juan, A., Lolo, F., Andres-Manzano, M.J., Serrano, M., Van Ginderachter, J.A., and Andres, V. (2012a). In vivo inhibition of c-MYC in myeloid cells impairs tumor-associated macrophage maturation and pro-tumoral activities. *PLoS ONE* *7*, e45399.
- Pello, O.M., De Pizzol, M., Mirolo, M., Soucek, L., Zammataro, L., Amabile, A., Doni, A., Nebuloni, M., Swigart, L.B., Evan, G.I., et al. (2012b). Role of c-MYC in alternative activation of human macrophages and tumor-associated macrophage biology. *Blood* *119*, 411–421.
- Peyssonnaud, C., Datta, V., Cramer, T., Doedens, A., Theodorakis, E.A., Gallo, R.L., Hurtado-Ziola, N., Nizet, V., and Johnson, R.S. (2005). HIF-1alpha expression regulates the bactericidal capacity of phagocytes. *J. Clin. Invest.* *115*, 1806–1815.
- Poczobutt, J.M., Gijon, M., Amin, J., Hanson, D., Li, H., Walker, D., Weiser-Evans, M., Lu, X., Murphy, R.C., and Nemenoff, R.A. (2013). Eicosanoid profiling in an orthotopic model of lung cancer progression by mass spectrometry demonstrates selective production of leukotrienes by inflammatory cells of the microenvironment. *PLoS ONE* *8*, e79633.
- Qian, B.Z., and Pollard, J.W. (2010). Macrophage diversity enhances tumor progression and metastasis. *Cell* *141*, 39–51.
- Quail, D.F., and Joyce, J.A. (2013). Microenvironmental regulation of tumor progression and metastasis. *Nat. Med.* *19*, 1423–1437.
- Rath, M., Muller, I., Kropf, P., Closs, E.I., and Munder, M. (2014). Metabolism via Arginase or Nitric Oxide Synthase: Two Competing Arginine Pathways in Macrophages. *Front. Immunol.* *5*, 532.
- Ravindran, R., Khan, N., Nakaya, H.I., Li, S., Loebbermann, J., Maddur, M.S., Park, Y., Jones, D.P., Chappert, P., Davoust, J., et al. (2014). Vaccine activation of the nutrient sensor GCN2 in dendritic cells enhances antigen presentation. *Science* *343*, 313–317.
- Recalcati, S., Locati, M., Marini, A., Santambrogio, P., Zaninotto, F., De Pizzol, M., Zammataro, L., Girelli, D., and Cairo, G. (2010). Differential regulation of iron homeostasis during human macrophage polarized activation. *Eur. J. Immunol.* *40*, 824–835.
- Rius, J., Guma, M., Schachtrup, C., Akassoglou, K., Zinkernagel, A.S., Nizet, V., Johnson, R.S., Haddad, G.G., and Karin, M. (2008). NF-kappaB links innate immunity to the hypoxic response through transcriptional regulation of HIF-1alpha. *Nature* *453*, 807–811.
- Rivera, L.B., Meyronet, D., Hervieu, V., Frederick, M.J., Bergsland, E., and Bergers, G. (2015). Intratumoral myeloid cells regulate responsiveness and resistance to antiangiogenic therapy. *Cell Rep.* *11*, 577–591.

- Rodríguez-Espinosa, O., Rojas-Espinosa, O., Moreno-Altamirano, M.M., Lopez-Villegas, E.O., and Sanchez-Garcia, F.J. (2015). Metabolic requirements for neutrophil extracellular traps formation. *Immunology* *145*, 213–224.
- Rodríguez-Prados, J.C., Traves, P.G., Cuenca, J., Rico, D., Aragonés, J., Martín-Sanz, P., Cascante, M., and Bosca, L. (2010). Substrate fate in activated macrophages: a comparison between innate, classic, and alternative activation. *J. Immunol.* *185*, 605–614.
- Ruan, G.X., and Kazlauskas, A. (2013). Lactate engages receptor tyrosine kinases Axl, Tie2, and vascular endothelial growth factor receptor 2 to activate phosphoinositide 3-kinase/Akt and promote angiogenesis. *J. Biol. Chem.* *288*, 21161–21172.
- Ruffell, B., Chang-Strachan, D., Chan, V., Rosenbusch, A., Ho, C.M., Pryer, N., Daniel, D., Hwang, E.S., Rugo, H.S., and Coussens, L.M. (2014). Macrophage IL-10 blocks CD8+ T cell-dependent responses to chemotherapy by suppressing IL-12 expression in intratumoral dendritic cells. *Cancer Cell* *26*, 623–637.
- Ryu, Y.K., Lee, M.H., Lee, J., Lee, J.W., Jang, S.J., Kang, J.H., and Moon, E.Y. (2015). gamma-Irradiated cancer cells promote tumor growth by activation of Toll-like receptor 1-mediated inducible nitric oxide synthase in macrophages. *J. Leukoc. Biol.* *97*, 711–721.
- Sag, D., Carling, D., Stout, R.D., and Suttles, J. (2008). Adenosine 5'-monophosphate-activated protein kinase promotes macrophage polarization to an anti-inflammatory functional phenotype. *J. Immunol.* *181*, 8633–8641.
- Saxena, V., Ondr, J.K., Magnusen, A.F., Munn, D.H., and Katz, J.D. (2007). The countervailing actions of myeloid and plasmacytoid dendritic cells control autoimmune diabetes in the nonobese diabetic mouse. *J. Immunol.* *179*, 5041–5053.
- Schmid, M.C., Avraamides, C.J., Dippold, H.C., Franco, I., Foubert, P., Ellies, L.G., Acevedo, L.M., Manglicmot, J.R., Song, X., Wrasidlo, W., et al. (2011). Receptor tyrosine kinases and TLR/IL1Rs unexpectedly activate myeloid cell PI3kgamma, a single convergent point promoting tumor inflammation and progression. *Cancer Cell* *19*, 715–727.
- Schwabe, R.F., and Jobin, C. (2013). The microbiome and cancer. *Nat. Rev. Cancer* *13*, 800–812.
- Semenza, G.L. (2003). Targeting HIF-1 for cancer therapy. *Nat. Rev. Cancer* *3*, 721–732.
- Semenza, G.L., Roth, P.H., Fang, H.M., and Wang, G.L. (1994). Transcriptional regulation of genes encoding glycolytic enzymes by hypoxia-inducible factor 1. *J. Biol. Chem.* *269*, 23757–23763.
- Serafini, P., Mgebroff, S., Noonan, K., and Borrello, I. (2008). Myeloid-derived suppressor cells promote cross-tolerance in B-cell lymphoma by expanding regulatory T cells. *Cancer Res.* *68*, 5439–5449.
- Shalova, I.N., Lim, J.Y., Chittechath, M., Zinkernagel, A.S., Beasley, F., Hernandez-Jimenez, E., Toledano, V., Cubillos-Zapata, C., Rapisarda, A., Chen, J., et al. (2015). Human monocytes undergo functional re-programming during sepsis mediated by hypoxia-inducible factor-1alpha. *Immunity* *42*, 484–498.
- Sharda, D.R., Yu, S., Ray, M., Squadrito, M.L., De Palma, M., Wynn, T.A., Morris, S.M., Jr., and Hankey, P.A. (2011). Regulation of macrophage arginase expression and tumor growth by the Ron receptor tyrosine kinase. *J. Immunol.* *187*, 2181–2192.
- Shime, H., Yabu, M., Akazawa, T., Kodama, K., Matsumoto, M., Seya, T., and Inoue, N. (2008). Tumor-secreted lactic acid promotes IL-23/IL-17 proinflammatory pathway. *J. Immunol.* *180*, 7175–7183.
- Siska, P.J., and Rathmell, J.C. (2015). T cell metabolic fitness in antitumor immunity. *Trends Immunol.* *36*, 257–264.
- Srivastava, M.K., Sinha, P., Clements, V.K., Rodriguez, P., and Ostrand-Rosenberg, S. (2010). Myeloid-derived suppressor cells inhibit T-cell activation by depleting cystine and cysteine. *Cancer Res.* *70*, 68–77.
- Stuehr, D.J., and Nathan, C.F. (1989). Nitric oxide. A macrophage product responsible for cytostasis and respiratory inhibition in tumor target cells. *J. Exp. Med.* *169*, 1543–1555.
- Tannahill, G.M., Curtis, A.M., Adamik, J., Palsson-McDermott, E.M., McGettrick, A.F., Goel, G., Frezza, C., Bernard, N.J., Kelly, B., Foley, N.H., et al. (2013). Succinate is an inflammatory signal that induces IL-1beta through HIF-1alpha. *Nature* *496*, 238–242.
- Tran Janco, J.M., Lamichhane, P., Karyampudi, L., and Knutson, K.L. (2015). Tumor-infiltrating dendritic cells in cancer pathogenesis. *J. Immunol.* *194*, 2985–2991.
- Traversari, C., Sozzani, S., Steffensen, K.R., and Russo, V. (2014). LXR-dependent and -independent effects of oxysterols on immunity and tumor growth. *Eur. J. Immunol.* *44*, 1896–1903.
- Valencia, T., Kim, J.Y., Abu-Baker, S., Moscat-Pardos, J., Ahn, C.S., Reina-Campos, M., Duran, A., Castilla, E.A., Metallo, C.M., Diaz-Meco, M.T., and Moscat, J. (2014). Metabolic reprogramming of stromal fibroblasts through p62-mTORC1 signaling promotes inflammation and tumorigenesis. *Cancer Cell* *26*, 121–135.
- van der Windt, G.J., Everts, B., Chang, C.H., Curtis, J.D., Freitas, T.C., Amiel, E., Pearce, E.J., and Pearce, E.L. (2012). Mitochondrial respiratory capacity is a critical regulator of CD8+ T cell memory development. *Immunity* *36*, 68–78.
- Vats, D., Mukundan, L., Odegaard, J.I., Zhang, L., Smith, K.L., Morel, C.R., Wagner, R.A., Greaves, D.R., Murray, P.J., and Chawla, A. (2006). Oxidative metabolism and PGC-1beta attenuate macrophage-mediated inflammation. *Cell Metab.* *4*, 13–24.
- Wang, R., Dillon, C.P., Shi, L.Z., Milasta, S., Carter, R., Finkelstein, D., McCormick, L.L., Fitzgerald, P., Chi, H., Munger, J., and Green, D.R. (2011). The transcription factor Myc controls metabolic reprogramming upon T lymphocyte activation. *Immunity* *35*, 871–882.
- Ward, P.S., and Thompson, C.B. (2012). Metabolic reprogramming: a cancer hallmark even warburg did not anticipate. *Cancer Cell* *21*, 297–308.
- Wise, D.R., DeBerardinis, R.J., Mancuso, A., Sayed, N., Zhang, X.Y., Pfeiffer, H.K., Nissim, I., Daikhin, E., Yudkoff, M., McMahon, S.B., and Thompson, C.B. (2008). Myc regulates a transcriptional program that stimulates mitochondrial glutaminolysis and leads to glutamine addiction. *Proc. Natl. Acad. Sci. USA* *105*, 18782–18787.
- Xue, J., Schmidt, S.V., Sander, J., Draffehn, A., Krebs, W., Quester, I., De Nardo, D., Gohel, T.D., Emde, M., Schmildeithner, L., et al. (2014). Transcriptome-based network analysis reveals a spectrum model of human macrophage activation. *Immunity* *40*, 274–288.
- Yang, M., Ma, C., Liu, S., Shao, Q., Gao, W., Song, B., Sun, J., Xie, Q., Zhang, Y., Feng, A., et al. (2010). HIF-dependent induction of adenosine receptor A2b skews human dendritic cells to a Th2-stimulating phenotype under hypoxia. *Immunol. Cell Biol.* *88*, 165–171.
- Zhang, Y., Sun, Y., Rao, E., Yan, F., Li, Q., Silverstein, K.A., Liu, S., Sauter, E., Cleary, M.P., and Li, B. (2014). Fatty acid-binding protein E-FABP restricts tumor growth by promoting IFN-beta responses in tumor-associated macrophages. *Cancer Res.* *74*, 2986–2998.
- Zhu, Y.P., Brown, J.R., Sag, D., Zhang, L., and Suttles, J. (2015). Adenosine 5'-monophosphate-activated protein kinase regulates IL-10-mediated anti-inflammatory signaling pathways in macrophages. *J. Immunol.* *194*, 584–594.